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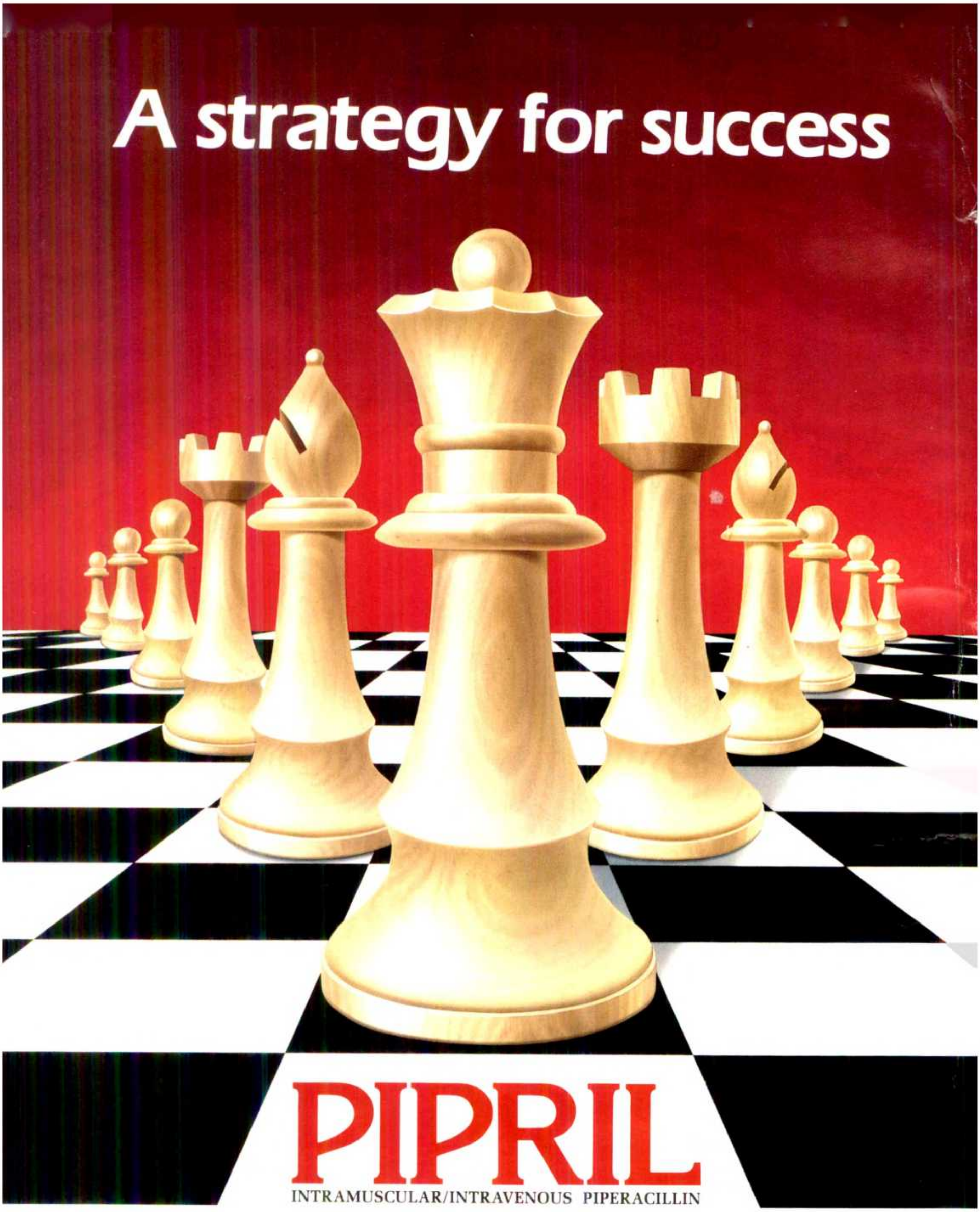

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Br. J. Surg. 1990, Vol. 77, January, 1–2

Gastrin and gastrinomas

Twenty-five years ago Gregory and Tracy identified two heptadecapeptides, gastrin I and II, from the antral mucosa of hogs. Drs Robert Zollinger and Edwin Ellison in 1955 published clinical details of two patients with fulminating peptic ulcer disease. Each patient was found to have a non-β cell pancreatic adenoma – one uncovered at post-mortem and the other at laparotomy for persistent ulceration. An abnormal protein was identified from one of the pancreatic tumours which was shown to have hyperglycaemic properties and it was thought to be similar to glucagon. Zollinger and Ellison correctly assumed that there was a 'hormonal or chemical stimulation of the gastric glands'[1]. They went so far as to suggest examination of the pancreas in those patients with uncontrolled or atypical primary peptic ulceration; 'Even resection of the body and tail of the pancreas might well be considered ... before subjecting the patient to total gastectomy'.

It has to be acknowledged that gastrinomas are very rare. Insulinomas, the commonest pancreatic endocrine tumour, are said to occur annually at less than one case per million[2]. Gastrinomas can occur sporadically or in combination with other endocrine tumours in a familial setting, the so-called Multiple Endocrine Neoplasia type I (MEN–I) syndrome. Hyperparathyroidism is the commonest endocrine abnormality in this setting but the use of gastrin determinations in a population of patients with primary hyperparathyroidism does nothing more than reveal a significant population of elderly females with hypo- or achlorhydria and secondary hypergastrinaemia[3]. Screening is not fruitful in this population. Similarly gastrin has no known role in the aetiology of uncomplicated peptic ulcer disease. Indeed the early symptoms of the Zollinger–Ellison syndrome is so like uncomplicated peptic ulcer disease that these tumours may escape detection in patients receiving today's effective long-term ulcer therapy.

Acknowledging the rarity of many endocrine tumours the surgeon must balance awareness of the condition with a healthy index of suspicion. Hypergastrinaemia (fasting level >1000 pg/ml) and gastric acid hypersecretion (basal acid output >15 mmol/h) in a patient with peptic ulcer disease go a long way towards satisfying diagnostic criteria.

Provocative tests with measurement of gastrin response are used to confirm less convincing biochemical values. Secretin is a potent gastrin secretagogue and probably works by a direct stimulatory effect on the gastrinoma cell by modulation of adenylate cyclase, probably by guanine nucleotide-binding proteins. False positive elevations in gastrin levels can be encountered and we have demonstrated that a rapid infusion of secretin and calcium gives no false positive or false negative results when the criteria for diagnosis are a 50 per cent increase or a 200 pg/ml increase above basal gastrin level[4]. Serum pepsinogen I is a marker for inherited peptic ulcer disease. It has been shown to be a reliable marker for Zollinger–Ellison syndrome in patients from MEN–I families. It appears not to be inherited as a genetic trait *per se* but is elevated secondary to chronic hypergastrinaemia[5].

Once a diagnosis is established then preoperative localization is usually undertaken. It is likely that gastrinomas are being diagnosed at an earlier stage than previously and the tumours will be correspondingly smaller. Thompson *et al.* have shown that the syndrome can be produced from lesions 2 mm in diameter which need not be in the pancreas[6]. In their hands transhepatic venous sampling was found to be a useful procedure for localization although the smaller extrapancreatic lesions could often only be found by duodenotomy and intraluminal exploration. Selective arteriography and computed tomography scans, with or without contrast enhancement, will localize some tumours. The combined use of endoscopic retrograde cholangiopancreatography with digital subtraction imaging in which a negative 'image' is produced by the tumour within the pancreatic parenchymogram may allow tumour localization. Intraoperative, high resolution, real-time ultrasound will allow detection of small lesions within the pancreatic parenchyma which might not be felt even when the pancreatic head is fully mobilized and palpated[7].

Even in institutions dealing with significant numbers of patients with gastrinomas, as many as 27 per cent will have a negative laparotomy and 40 per cent of biochemically cured patients will continue to hypersecrete acid[8]. H_2-receptor antagonists

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(cimetidine, ranitidine or famotidine) or an H^+-K^+-ATPase blocking agent (omeprazole) will provide good long-term medical control of continued hypersecretion of acid. A somatostatin analogue, such as SMS-201-995 or octreotide (Sandoz Pharmaceuticals Corporation, East Hannover, New Jersey, USA) diminishes hypersecretion of gastrin and gastric acid in the long-term and may even change tumour capacity to release gastrin[9]. Whichever long-term antisecretory medication is used repeated endoscopy and biopsy is necessary since argyrophil cells proliferate with the occasional production of gastric carcinoids.

Eighty-five per cent of gastrin-producing tumours occur in the pancreas – an organ in which G cells are not normally found. It is hypothesized that pancreatic gastrinomas originate from inappropriate differentiation of multipotent endocrine stem cells. This might explain the heterogeneous cell types of pancreatic gastrinomas as well as their higher malignancy rate compared with gut gastrinomas. This variable pathology with variations in tumour site make it impossible to be dogmatic about appropriate surgical treatment. Because of the efficiency with which acid secretion can be blocked the place of total gastrectomy is questioned. Indeed the combination of conservative surgery (simply excision or shelling out of macroscopic tumours) in well-differentiated extrapancreatic gastrinomas with nodal metastases and with adjunctive ranitidine allows excellent survival associated with symptom control. It is suggested that lymph node gastrinomas are usually metastatic from primary duodenal lesions (if the primary is not obvious), and that nodal disease may occur as a primary phenomenon. Whether primary or not lymph node gastrinomas have a good prognosis (about 80 per cent 20-year survival rate), and so this finding should not deter aggressive surgical treatment[10]. In the MEN–I syndrome, however, total pancreatectomy has been advocated because in this syndrome multiple tumours may be present (nearly always in the pancreas), further tumours may arise in the pancreatic remnant and, especially with gastrinomas (as distinct from insulinomas), metastasis to the liver is a common occurrence[11].

Although the Zollinger–Ellison syndrome is over 30 years old, we have not heard the end of the gastrin story. Remain suspicious and refer appropriately. Only from centralized and accumulated experience of these fascinating clinical problems will we learn more of the biology of gastrin function and perhaps of the process of neoplasia.

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Br. J. Surg. 1990, Vol. 77, January, 3–4

The need for a Chair of Tropical Surgery

Over half of the world's population lives in the tropics. Surgery there is markedly different in terms of the underlying pathology, patient presentation and management, but its study and practise is fascinating and rewarding. There is enormous potential for research. The surgical need is unparalleled, and alongside this is a need for appropriate training of nationals from these countries. Western countries with their long surgical tradition and resources can make a very real contribution to surgical care in the tropics, at the same time enhancing and broadening the skills of their surgeons.

There are many distinctly tropical surgical conditions, such as tropical pyomyositis, madura foot, cancrum oris, tropical skin ulcers, and the sequelae of polio and leprosy. Other conditions which occur infrequently in the West but are common in the tropics include keloids, postgonococcal urethral stricture and chronic lymphoedema. Tropical surgery can justifiably be considered as a distinct subspecialty of surgery.

Patient presentation is distinctive because it is frequently late. Tumours are advanced, acutely ill patients are often moribund, and fractures may be accompanied by osteomyelitis or gangrene. Management is modified by economic constraints; complex and expensive techniques of investigation and treatment are often possible but only at the expense of not treating other patients, often those who are poorest and most in need. There is a desperate need for appropriate surgery, applicable and available to the whole population. Careful management of resources of the Government and the patient (who may be spending his whole year's income on his operation) must be part of everyday surgical practice.

In the past Western surgeons have made a major contribution to the surgical services of many tropical countries. In these days of special interests and subspecialization it would seem an attractive concept for an academic department of surgery in the West to have tropical surgery as one of its areas of special interest and establish links with departments of surgery in the tropics. I would like to suggest four areas in which an academic department of surgery could contribute: in the appropriate training of overseas graduates; in the practical encouragement of surgeons in the tropics; by encouraging surgical research in the tropics; and by arranging and overseeing surgical elective secondments and/or exchanges to the tropics.

Many overseas surgeons do part of their postgraduate training in the West but such trainees are often ill equipped to return to their own countries; many are incapable of working without the facilities available to Western surgeons, and are unable to adapt their new found knowledge to their home environment. Despite many surgeons having been trained for the tropics, the provision of surgical care for the general population in many tropical countries has improved little. Nordberg, for example, estimated that only 10–15 per cent of patients who required repair of inguinal hernia were operated upon in East Africa[1].

In the UK the fellowship examination is an entry qualification to higher surgical training, whereas in the tropics it is often seen as an 'exit' examination indicating the completion of training. The surgeon may well be appointed as a consultant on his return home and will be working without supervision. We must train surgeons to meet these challenges. Those formulating postgraduate training for overseas graduates need to have practical experience of tropical surgery so that it is as appropriate as possible. The Overseas Doctors Training Schemes run by the Royal Colleges of Surgeons in Britain represent a very positive step forward. Such schemes would be further bolstered by the support of an academic department of tropical surgery.

One of the great problems of surgical care in the tropics is the need to make it available to the whole population, and it is difficult to keep surgeons working in rural areas where they feel professionally and socially isolated[2]. An academic department of tropical surgery could establish links not only with existing centres of excellence but also with rural hospitals, so as to increase both the prestige and job satisfaction of these posts[3]. The amount of support needed would vary, ranging from the occasional letter to professional visits, exchanges and further postgraduate training. Visits from senior colleagues are particularly encouraging, whether for a sabbatical year or only a few weeks, and I suspect that many surgeons would be happy to spend their annual leave combining 'business' with pleasure. The Royal Colleges in Britain are already involved in encouraging and helping with indigenous

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programmes of postgraduate surgical training and this is a further area where an academic department of tropical surgery might contribute.

Collaboration can never be a one-way process, and research is an excellent example of this. Research is now a standard part of surgical training and there is great scope in the tropics for clinically applied, practical, research. In many areas the pattern and incidence of surgical diseases, let alone their aetiology and management, have still to be documented. There are practical difficulties; back up and laboratory facilities are often inadequate, but these difficulties could be overcome by links with a department in a Western country, so that advice and, on occasions, technical help may be offered.

Western graduates could benefit from further training in the tropics and surely there are ways in which surgical training could be made more flexible so that overseas experience might be seen as an added strength. The clinical and operative experience gained overseas is invaluable; the trainee is likely to be able to tackle a wide range of surgical pathology and so develop and broaden his clinical, diagnostic and operative skills[4]. The resourcefulness and independence developed is a valuable asset to the surgeon and to the National Health Service to which he will return. In addition he will often gain experience in administration and personnel management[4], experience which is difficult to obtain in countries such as Britain during training, but which is of increasing importance. Ideally a tropical post would be part of a post-fellowship teaching hospital surgical rotation. During occupancy of this post the trainee would complete a research project, and keep a log book of his clinical and operative experience. This would ensure appropriate and properly supervised posts and give the overseas experience more credibility.

The establishment of formal links between departments of surgery in Western countries and in the tropics would benefit surgeons in both. The challenge of providing good surgical care is one in which we should give our overseas colleagues all the help we can. The time is ripe for a Chair of Surgery with an interest in tropical surgery.

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Review

Br. J. Surg. 1990, Vol. 77, January, 5–12

Surgical management of acute pancreatitis

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This review examines the lack of improvement in terms of mortality and outcome in patients with acute pancreatitis. Energetic fluid replacement is the only treatment of proven value. There is a strong case for identification of patients with severe disease who may benefit from early operative intervention. Eradication of gallstones may prevent further attacks in patients with gallstone pancreatitis. The benefits of pancreatic resection and necrosectomy still require full evaluation.

Keywords: Acute pancreatitis, mortality, non-operative treatment, surgery

Acute pancreatitis has progressively increased in incidence over the last 40 years in Britain[1–5]. Part of this increase could be artificial, reflecting better recognition of the disease because serum amylase is measured routinely in patients with unexplained acute abdomen. Were this the case, the number of patients with a severe attack would be diluted by those with mild ('biochemical') disease. However, careful analysis of the data in Bristol shows that the proportion of fatal attacks has remained at the same level (*Table 1*) between 1950 and 1980[4], from which we conclude that there has been a genuine increase in incidence.

The common predisposing causes of acute pancreatitis are well documented, notably gallstones and alcoholism (*Table 1*). Less clearly understood is the pathogenesis of the disease[6], that is the mechanisms leading to acinar rupture and release of activated enzymes within the parenchyma of the gland. Duodenopancreatic reflux, papillary obstruction and pancreatic hypersecretion have all been proposed[6]. Each mechanism is plausible, none on its own explains all the facts, and the three could well be interlinked; moreover some agents can probably damage the gland directly.

Several questions remain unanswered. Does oedematous pancreatitis always precede haemorrhagic pancreatitis, because, if so, timely and appropriate therapy might arrest this disastrous process? Could gallstone pancreatitis and alcoholic pancreatitis have a common pathogenesis, such as papillary inflammation? Should our concept of acute alcoholic pancreatitis be confined to attacks of pain and hyperamylasaemia occurring in a person with pre-existing structural damage to the pancreas induced by alcohol? When the causation is so obscure, it is little wonder that the treatment remains empirical and largely supportive in nature.

Since patients with acute pancreatitis present with abdominal pain, they are often admitted to a surgical ward. We believe that this is the most appropriate place to manage these patients because there are several indications for operation in this disease. This review will outline the initial assessment of a patient with acute pancreatitis and the basic treatment, before concentrating on the indications for operation and the role of the surgeon in management.

The initial assessment

Methods of diagnosis

Most British authors accept a fourfold elevation in serum amylase (i.e. 1200 units/l) as diagnostic of acute pancreatitis in patients who present with acute abdominal pain[7–9]. However, intra-abdominal catastrophes (e.g. perforation, trauma, intestinal obstruction or infarction) and metabolic problems (hypothermia, diabetic ketoacidosis, uraemia) may cause transient hyperamylasaemia[10,11], while even this level will miss some genuine cases of pancreatitis. No other enzyme has proved superior in routine practice. Gallstones are responsible for 50–60 per cent and alcohol for 8–32 per cent of attacks of acute pancreatitis in Britain[1]. Ultrasonography will detect gallstones in two-thirds of cases of gallstone pancreatitis, when used early after admission to hospital[7]. Endoscopic retrograde cholangiopancreatography (ERCP) will detect gallstones in as many as 76 per cent (100/131) of patients with predicted severe attacks of pancreatitis in whom cholelithiasis is suspected[12]. The only technique with a higher specificity is sieving the stools for stones during the recovery period[13].

Determination of severity

Although the total amylase content of the blood remains the diagnostic yardstick in routine clinical practice[14], it is generally acknowledged that the degree of elevation of the enzyme does not correlate with the severity of the disease[7]. Yet early identification of those patients (about 25 per cent) with a severe and potentially lethal attack is particularly desirable. This group of patients should be followed with much closer scrutiny than might be appropriate for the majority who recover quickly. Identification would allow better allocation of intensive care facilities and help to identify those patients requiring early operative intervention. Unfortunately clinical assessment of severity is notoriously unreliable during the crucial first 48 h of the attack, though certain physical signs (profound shock, tetany and abdominal mass) are grave portents when present.

We have recently reviewed methods for the early assessment of acute pancreatitis[7]. In brief, several individual markers, such as methaemalbumin, fibrinogen, endotoxin and complement proteins[7,15], are too insensitive for routine clinical practice.

Table 1 *Aetiological causes of acute pancreatitis in Bristol*

	First attacks		Recurrent attacks	
	Cases	Deaths	Cases	Deaths
Gallstones	319	41	41	4
Alcoholism	51	7	13	0
Idiopathic	146	29	21	5
Postoperative	20	11	0	0
Neoplasia	11	9	0	0
Miscellaneous	44	19	3	1
Unknown	45	9	2	2
Total	636	125 (19.7%)	80	12 (15%)

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Hypocalcaemia and hypoxaemia are also fallible, but they do have the advantage of indicating a therapeutic need[9,16]. Urgent contrast-enhanced computed tomography (CT) may differentiate between the mild (oedematous) and severe (haemorrhagic) forms of acute pancreatitis[17,18]. However, it does not improve on scoring systems for the prediction of disease severity[19], and there may be logistic problems in performing a routine CT scan at the outset, its value in the later management of pancreatic abscess and/or necrosis is undisputed[20,21]. Measurement of C-reactive protein is certainly simpler, and it may turn out to be the best discriminant between mild and severe attacks[22].

Scoring systems based on multiple laboratory criteria[23,24] are able to detect severe (i.e. complicated) attacks of acute pancreatitis in quite a high percentage of cases, for example 61 per cent in our own experience[25] Although it takes 48 h to obtain a full set of data in equivocal cases, a 'positive' score is rapidly available in fulminant disease The criteria outlined by Ranson and Imrie are well established on an international basis and are therefore useful in assessing and comparing the response to different therapeutic regimens[23,24]. However, care should be taken in interpreting a low serum albumin as a prognostic marker, since the threshold value varies with the methodology of the assay[26] Recently, good correlation has been made with outcome by using the acute physiology and chronic health evaluation (APACHE) scoring system shortly after admission[27].

A quicker assessment of severity can be obtained by abdominal paracentesis and examination of the free peritoneal fluid[28]. The risk of inadvertent visceral puncture (1 per cent) is balanced by the occasional discovery of other causes of an acute abdomen, such as biliary peritonitis (free bile) and leaking aneurysm (free blood)[25]. Nevertheless, it is probably not justifiable to insert routinely a peritoneal dialysis catheter unless major therapeutic decisions depend on the result. By combining clinical judgements, multiple laboratory criteria and abdominal paracentesis, we were able to identify 77 per cent of all severe attacks, this figure rising to 85 per cent of lethal attacks and to 95 per cent of those causing death within the first 10 days[25].

Non-operative treatment

For the substantial majority of patients with acute pancreatitis treatment is conservative The patient is given nil by mouth with nasogastric aspiration (although there is little evidence that this is beneficial[29]) and fluid replacement until the 'pancreatic burn' subsides, usually within seven days. Excessive fluid loss is a prognostic indicator of poor outcome[30] Adequate replacement of fluid, notably colloid, is the single most valuable measure, since up to one-third of plasma volume may be sequestered in the third space during an attack of acute pancreatitis[31]. Central venous pressure should be monitored at the first sign of hypovolaemia (hypotension, decreased urine output) and may be assisted by measurement of left atrial pressure[31]. Antibiotics should probably be reserved for proven sepsis such as cholangitis and septicaemia. Arterial gas measurements should be made at least daily in the first 48 h and oxygen should be given routinely by mask at the first sign of hypoxaemia In experimental animals it has been shown that substantial deterioration in pulmonary vascular resistance needs to occur before arterial oxygen tension falls[32], so that great care must be taken in interpreting apparently normal blood gas results.

The search continues for an effective drug against acute pancreatitis. Laboratory studies with somatostatin[33] and early clinical trials using somatostatin analogues[34] have suggested some improvement in outcome if the agent is given early in the acute attack, but these findings need corroboration. Promising experimental results with prostaglandins[35] have not been followed up with controlled clinical studies in man, and prospective clinical trials do not support the routine use of glucagon or aprotinin (Trasylol®, Bayer, Newbury, UK)[24] The similar failings of peritoneal lavage are considered below Early reports of good results using fresh frozen plasma (FFP) as a natural source of antiprotease activity in acute pancreatitis were encouraging[36]. Although the recent Leicester study showed that FFP limited the fall of α_2-macroglobulin after the first day, it did not confirm any clinical benefit, possibly because two units per day of FFP does not affect the trypsin inhibitory capacity of the serum, which is already increased in severe acute pancreatitis[37]. For practical purposes, therefore no specific non-operative measures have yet been shown to improve the outcome in acute pancreatitis.

Operative treatment

Diagnostic operations

A modest elevation of serum amylase (500–1000 units/l) is not uncommon in various acute abdominal conditions, such as biliary peritonitis, perforated peptic ulcer, gangrenous intestine, high small bowel obstruction and leaking aortic aneurysm. Less often the degree of hyperamylasaemia would ordinarily be sufficient to sustain a diagnosis of acute pancreatitis, but certain features raise doubt in the clinician's mind, for example marked jaundice, hyperactive bowel sounds, evidence of blood loss or a strong history of peptic ulcer disease. Plain abdominal X-rays, ultrasonography, CT scan and especially paracentesis (which should precede laparotomy in these cases) may clarify the diagnosis, but otherwise the surgeon should proceed to laparotomy without delay. The evidence shows that whereas most of these mimicking diseases are lethal without prompt operative treatment, diagnostic laparotomy does not exacerbate the attack of acute pancreatitis[38,39], although it may be associated with an increased incidence of subsequent pancreatic infection, particularly in severe pancreatitis[40]

The operative evidence of acute haemorrhagic pancreatitis is quite clear-cut, namely fat necrosis, retroperitoneal induration and discoloration, blood-stained ascites and a swollen pancreas. A full laparotomy should always be carried out, with particular attention to the gallbladder and duodenum and to the lesser sac, if a diagnosis is not immediately apparent. The correct procedure to adopt if acute pancreatitis is encountered is still a matter of some controversy. Our own policy is to search for and deal with gallstones but to leave the pancreas alone Cholecystectomy is generally straightforward, but inflammation spreading from the head of the pancreas into the free edge of the lesser omentum can hamper exposure of the bile duct and duodenal mobilization. If at all possible cholangiograms should be obtained, preferably using fluoroscopy and half-strength contrast for the best demonstration of small stones within the biliary tree. Ductal calculi should be gently removed. If the pancreatitis is not too severe, there is no contraindication to full exploration of the common bile duct including choledochoscopy and, if necessary, transduodenal sphinteroplasty to release a calculus wedged in the ampulla (as advocated by Acosta)[41] In the presence of severe haemorrhagic pancreatitis transduodenal sphincteroplasty runs the risk of duodenal fistula. Nevertheless, a dilated common bile duct should always be decompressed to reduce the risk of ascending cholangitis and septicaemia, simple insertion of a T tube will achieve this goal

At the completion of a diagnostic laparotomy for acute pancreatitis a Tenschkoff-type catheter may be inserted for peritoneal lavage. Despite a promising pilot study[38], the three-centre British trial of peritoneal lavage in 91 patients with severe acute pancreatitis failed to show any improvement in outcome, using hourly cycles of 2 litres of dialysate continued for 72 h (Reference 42) The series included 24 patients with acute alcoholic pancreatitis and a subgroup in which benefit had previously been reported[43]. However, antibiotics were not included in the lavage solution, so that the higher incidence of bacterial peritonitis among lavaged patients than controls (5 *versus* 1) might conceivably have negated any slight advantage of dialysis. The release of proteolytic enzymes into the peritoneal cavity and the subsequent activation of complement C_3 and associated kinins provide theoretical support for lavage (with or without additives), particularly since peritoneal fluid from pancreatitis patients is toxic both *in vivo* and *in vitro*[44] Thus, the safe, open insertion of a dialysis catheter remains of potential value as long as it is managed aseptically. It does provide access for peritoneal dialysis should renal failure develop, though increased protein loss is an inevitable consequence of lavage and requires adequate intravenous replacement[42].

Prophylactic operations

The most effective means of preventing acute pancreatitis is to perform early cholecystectomy in patients with cholelithiasis. Symptomatic gallstones, especially if small and multiple, should be removed as soon as possible and preferably during the acute admission. The presence of gallstones should be rigorously sought in every patient who presents with acute pancreatitis, including those with alcohol-associated disease. Especially in women, one negative ultrasound scan in inadequate The test should be repeated, together with oral cholecystography, when liver function tests return to normal As already stated, the most certain way of detecting the causative gallstone is to sieve the stools during convalescence[12].

Biliary surgery should be carried out at an early stage after an attack of acute pancreatitis, although not urgently[45–48]. We advocate gallbladder ultrasonography within the first few days of the attack and proceed to cholecystectomy during the same admission, generally some 5–15 days after the onset of symptoms. If the operation is carried out any earlier, postoperative complications are more common[45–47] Very early operations are also associated with a significant negative laparotomy rate owing to erroneous diagnosis of gallstones and cholecystitis[49]. If operation is deferred to a subsequent hospital admission, there is a 32–48 per cent chance of recurrent pancreatitis while the patient remains on the waiting list[7]. Operative cholangiography is an essential part of cholecystectomy after pancreatitis, although the incidence of ductal calculi diminishes rapidly as the acute attack recedes. Common bile duct gallstones can be demonstrated in 18 per cent of patients with biliary pancreatitis overall[49], though impacted stones are only found in about 4 per cent of patients with acute pancreatitis undergoing autopsy[50].

A good case can be made for performing ERCP after any attack of 'idiopathic' pancreatitis, and the investigation is mandatory in recurrent disease. ERCP can reveal a wide range of lesions that are amenable to surgical correction, including unsuspected gallstones, congenital anomalies (pancreas divisum, choledochal cyst), stenosis or ectasia of the pancreatic duct[51] and carcinoma of the ampulla[52]. Cotton demonstrated the congenital anomaly of pancreas divisum in 20 of 78 (26 per cent) patients with unexplained recurrent pancreatitis[53] as opposed to 6 of 169 (3·6 per cent) 'controls' with primary biliary tract disease. The association remains controversial, because a large Belgian series of patients with pancreas divisum ($n = 304$) showed no link between the presence of the anomaly divisum and any type of pancreatitis[54] A tiny outlet for the bulk of the pancreatic secretion might predispose to pancreatitis in such patients, yet pancreas divisum could also be expected to protect the dorsal pancreas from the effect of gallstone impaction at the major papilla We have successfully treated two patients with recurrent pancreatitis by means of (operative) accessory sphincteroplasty[55] The much larger experience of Warshaw *et al.* indicates that the patients who benefit most from accessory sphincteroplasty are those with recurrent acute pancreatitis (as opposed to chronic pain), stenosis of the duct of Santorini and also those with no radiological evidence of chronic pancreatitis[56].

Sometimes, ERCP will demonstrate pancreatic ductal ectasia and/or stenosis at the origin of the duct of Wirsung[51]. In such cases inflammatory scarring could emanate from one attack of acute pancreatitis and predispose to another. Operative drainage of the duct, either by double sphincteroplasty or longitudinal pancreaticojejunostomy (depending on the anatomy of the ductal tree), may limit further attacks of pancreatitis[55]

Hyperparathyroidism is often cited as a cause of acute pancreatitis[57–59]. In our own experience there were only 2 cases of hyperparathyroidism among 650 patients presenting with acute pancreatitis[4]. Since routine serum calcium assays now yield 13 000 new cases of hyperparathyroidism annually in Britain, most of whom are asymptomatic[60], it is inevitable that the two diseases sometimes coexist[58]. Nevertheless, parathyroidectomy seems advisable in such patients since a causal relationship has not been disproved.

Stone and colleagues have advocated truncal vagotomy plus Billroth II (Polya) partial gastrectomy for recurrent acute pancreatitis in alcoholism[61]. Both the vagal denervation and the redirection of gastric contents away from the duodenum (reducing duodenal cholecystokinin release) may lower pancreatic exocrine secretion However, the disadvantages of gastrectomy may outweigh the advantages of the procedure in alcoholics who continue to drink[62]. In any case pancreatic secretion should be maintained by the jejunal release of cholecystokinin[63] and secretin[64].

Therapeutic operations

In a small proportion of patients, acute pancreatitis is clearly fulminant from the outset or there is early clinical deterioration despite full supportive measures In these cases it is tempting to operate, to try and interrupt the remorseless progress of the disease and avert death. Opie's findings that lethal attacks of pancreatitis are sometimes associated with calculi impacted at the ampulla[65,66] affords a potential justification for early incision of the papilla in every case of gallstone-related disease. Operative manoeuvres undertaken within 2–3 days of admission to hospital and before the development of 'surgical' complications (see below) may reasonably be termed therapeutic. One such procedure involves decompression of the biliary tree (cholecystostomy) and stomach (gastrostomy) plus insertion of a feeding jejunostomy tube[6]; the operation is of no proven benefit and obsolete. Likewise, early debridement of the pancreas is merely meddlesome. Thus current therapeutic operations are limited to sphincterotomy and pancreatic resection.

The questionable assumption that progression of disease stems from continued calculus obstruction is the basis for urgent *transduodenal sphincterotomy*. By adopting this policy Acosta *et al.* reduced the mortality rate of acute pancreatitis in Argentina from 16 to 2 per cent while the additional morbidity rate fell from 22 to 15 per cent[41]. However, the study employed unoperated historical controls for comparison All 46 patients submitted to operation within 48 h of admission had gallstones within the bile duct or stools, and stones were impacted in the ampulla in 72 per cent. Inevitably the retrieval rate would be much lower in other countries where gallstone disease is less predominant. A safer alternative nowadays is urgent *endoscopic papillotomy*[12,67–71], carried out after retrograde cholangiography has confirmed gallstones. However, in the hands of all but the most skilled operators there must be a potential hazard of exacerbating pancreatitis, especially if a 'pre-cut' is required to negotiate the catheter past the stone. Haemorrhage could obviously be fatal in patients who are already seriously ill.

Aside from technical considerations, there are two disadvantages to a policy of urgent papillotomy. First, at least one-third of cases of pancreatitis are not due to gallstones, and the urgent diagnosis of gallstones in acute pancreatitis is a fallible process[7]. Second, the criminal calculus may already have passed[72] Invasive cholangiography, either transpapillary or transhepatic, could determine both these points, but the hazards may not outweigh the benefits. Furthermore, even if the patient has persistent gallstone obstruction, will decompression necessarily abort the pancreatitic process? In fulminant pancreatitis irreversible pathological changes may already be present by the time such intervention is considered. Yet in any type of acute pancreatitis prompt disimpaction could prevent bacterial infection of the obstructed pancreas. A prospective randomized study of ERCP combined with endoscopic sphincterotomy (where indicated) during severe attacks of suspected gallstone pancreatitis showed that this approach resulted in fewer major complications (6 of 25 *versus* 17 of 28 controls), fewer deaths (1 *versus* 5) and a shorter hospital stay. These data from Leicester suggest that ERCP is of little benefit in predicted mild attacks, but that urgent sphinterotomy may improve outcome in patients with predicted severe attacks of gallstone pancreatitis[71].

Theoretically, adequate pancreatic drainage should involve sphincterotomy of the pancreatic duct itself, not just the bile duct Yet Stone *et al.* described a gush of pancreatic juice in patients with acute pancreatitis when the ampullary sphincter alone was divided and before septotomy was performed[72]. Although the gallstone had often passed already, dividing the oedematous sphincter was regarded as a valuable manoeuvre, with no associated worsening in outcome and reduction in both hospital stay and recurrent pancreatitis[72]. However, such a procedure is a major surgical intervention for a condition that may already be resolving spontaneously Endoscopic papillotomy seems a more attractive option, especially if further studies confirm its promise in reducing death from severe gallstone pancreatitis.

The major determinant of outcome in the early stages of acute pancreatitis is *recognition of pancreatic necrosis.* In a careful analysis of 205 patients operated for necrotizing pancreatitis, Beger and colleagues identified four factors with a direct bearing on outcome[73]. First, the extent of pancreatic necrosis; the mortality rate ranged from 7 per cent if <30 per cent of the gland was necrotic to 50 per cent if necrosis was subtotal or total. Second, the presence of extra pancreatic necrosis doubled the mortality rate from 15 to 34 per cent. Third, bacterial contamination more than trebled the mortality rate from 10 to 32 per cent. Fourth, the development of pancreatic ascites quadrupled the mortality rate from 9 to 36 per cent.

The generally accepted indications for early operation are a poor response to intensive supportive therapy, clinical deterioration, progression of organ failure, peritonitis and uncontrolled sepsis. There is some evidence that the extent to which phospholipase A_2, elastase and α-1-c protease are released can discriminate between oedematous and necrotizing pancreatitis[74–76]. Moreover, radiological interpretation of the extent of pancreatic necrosis on contrast-enhanced CT scan correlates well with the histological findings in the resected specimen[17–20]. Of course CT scan only shows the condition of the pancreas at that instant, so that the examination must be repeated if the clinical signs change

In 1963 Watts[77] reported the survival of one patient with fulminant pancreatitis after *total pancreatectomy.* Occasionally, oedema and vascular necrosis with thrombosis can make this a relatively straightforward procedure for the experienced surgeon[78]. Yet, the overall mortality rate is formidable, never less than 33 per cent and often approaching 100 per cent[76–81]. The major complications are haemorrhage, both primary and secondary, and continuing or subsequent sepsis[82]. The ultimate survivors, particularly the alcoholics, have serious problems with polyneuropathy and brittle diabetes[82] Apart from uncontrollable bleeding, the major operative problem lies in distinguishing viable pancreas from necrotic tissue Complete infarction of the pancreas is unlikely to occur, since total endocrine and exocrine pancreatic failure is exceptional among survivors of even the most fulminant pancreatitis. In any case surgeons are notoriously unreliable at identifying pancreatic necrosis[83,84].

In the presence of necrotizing pancreatitis, urgent *pancreatic sequestrectomy* may be safer than formal pancreatic resection and can produce mortality rates as low as 8–33 per cent[80,81,84,85], yet some surgeons believe that even this procedure is needlessly radical[86]. Others have advocated a combination of lesser sac lavage with debridement of necrotic pancreas[87], but a prospective study of 24 patients in Finland showed no benefit from lavage[88]. The development of extra pancreatic necrosis involving adjacent viscera is an absolute indication for laparotomy[89], but this is more appropriately considered in the next section

Surgical management of complications

Pseudocyst. Pancreatic pseudocysts are collections of fluid which has escaped from a pancreatic ductal tree disrupted by acute inflammation and/or obstructed by stricture or stone. In contrast to congenital and neoplastic cysts of the pancreas, they have no epithelial lining. The differential diagnosis of pseudocysts has recently been reviewed by Warshaw[90]. Loculated effusions rich in amylase can develop in the viscinity of the pancreas within 1–2 weeks of the acute attack[91,92]. A large pseudocyst will produce a palpable mass and cause renewed or persistent elevation of the serum amylase[93]. The cyst usually occupies the lesser sac but may form between the leaves of the greater or lesser omentum or between loops of small intestine. Occasionally it may lie further afield, beneath the diaphragm, extending into the pelvis or even within the mediastinum with associated mediastinitis[94]. Pseudocysts are more common in alcoholic pancreatitis than gallstones pancreatitis (15 *versus* 3 per cent), but haemorrhage and sepsis are more likely to complicate cysts associated with gallstones[9]; the incidence of these complications increases with the passage of time[95].

The evolving use of ultrasound and CT scan have shown that peripancreatic effusions develop after attacks of acute pancreatitis in as many as 20 per cent of cases, but more than half resolve spontaneously within 4–6 weeks[91,92]. Some authors draw a distinction between resolving ‘acute’ pseudocysts and those that mature and persist to become ‘chronic’ pseudocysts[96,97]. Serial CT scans allow the surgeon to follow the progress of a pseudocyst and determine the timing of drainage procedures.

Infection complicates 11 per cent of pseudocysts[98], either at the time of presentation or during subsequent observation of the lesion. Signs of infection such as pyrexia and positive blood cultures are a clear indication for urgent operation, which is associated with morbidity and mortality rates similar to those of elective decompression[92] (in sharp contrast to the outcome with a pancreatic abscess). Haemorrhage into the cyst is the most serious complication, carrying a mortality rate of 30–60 per cent[96–99]. Angiographic assessment during resuscitation is invaluable, and transcatheter embolization can be life-saving[100]. However the need to manage the pseudocyst as well as arrest the haemorrhage makes operative intervention the method of choice, with a mortality rate in experienced hands as low as 12·5 per cent[98]. Other complications of pseudocyst include spontaneous rupture into the abdominal cavity, with the development of pancreatic ascites, and obstruction of the duodenum or rarely the common bile duct[98].

The diagnosis and localization of pseudocysts traditionally depended upon radiographic delineation of extrinsic compression of the stomach, transverse colon, duodenum or kidney in a patient recovering from acute pancreatitis. These indirect techniques have been superseded by ultrasound and CT scanning. CT is more accurate than ultrasound, particularly for lesions adjacent to the tail of the pancreas, which often lie behind the transverse colon and stomach and are overshadowed by bowel gas[101–104]. CT also has the advantage of differentiating a mature pseudocyst with or without infection from a pancreatic abscess[9] Pseudocysts have a typical cavity filled with fluid or pus and surrounded by a discrete wall, whereas abscesses show as a swelling of the pancreas and adjacent tissues, i.e. a pancreatic phlegmon[105].

Although it has been customary to treat pseudocysts operatively, recent advances have allowed both percutaneous and endoscopic approaches to their management. The mortality rate of percutaneous drainage under ultrasound or CT control is low, but complications (chiefly cyst recurrence) exceed

50 per cent in incidence[98] Unfortunately, most reported series of percutaneous cyst drainage contain few patients[106–112], although a 66 per cent success rate among 22 patients has recently been reported from Lund in Sweden[113]. Recurrence is likely to necessitate repeated aspiration, with a cumulative risk of introducing infection into the cyst

Endoscopic drainage can be by the transgastric route using direct puncture through the stomach wall[114–116]. However, experience is limited to only a few centres, which are successful in about half the cases undertaken. Endoscopy also allows retrograde pancreatography to define ductal anatomy and possible ductal communication with the pseudocyst, which is said to occur in 20–60 per cent of cases[117–121]. ERCP also defines the origin of pancreatic ascites and pancreatic fistula, together with concomitant biliary lesions such as gallstones and bile duct stricture Biliary stricture is the usual cause of obstructive jaundice in pancreatitis, often mistakenly ascribed to extrinsic compression by the pseudocyst[121,122] Since ERCP can exacerbate acute pancreatitis and cause bacterial contamination of the pseudocyst, it should be judiciously employed and co-ordinated with planned surgical exploration

At present there is no evidence that either percutaneous or endoscopic drainage is superior to an operation that achieves internal drainage of the pseudocyst. Operative drainage is much more likely to clear the debris that often accompanies these fluid collections. Although sometimes necessary for immature cysts, operative external drainage is analogous to percutaneous drainage and carries a similar complication rate of 55 per cent, including a 30–40 per cent chance of recurrence and a 20–40 per cent chance of infection of the cyst cavity[92,96]. Where possible, most surgeons prefer to wait 4–6 weeks until the cyst develops a thick lining and then perform an internal drainage procedure, ideally with anastomosis of the mature cyst wall to a Roux loop of jejunum[6]. Cystgastrostomy is less satisfactory in our opinion. the cyst may not be closely applied to the back of the stomach or may extend for several centimetres below its lower border, preventing safe dependent drainage if the transgastric route is employed. Certain complications such as bleeding and gastric fistula may also be more common[6,122]

Multiple pseudocysts occur in 15–25 per cent of cases and usually reflect loculation of the original collection; even if they are discrete, they often lie adjacent to one another In either case they can be managed by internal cystocystostomies, with dependent drainage of the lowermost cyst to a Roux loop[123] Pseudocyst recurrence is usually associated with an inadequate drainage procedure or, in alcoholics, with continued alcohol abuse[124].

Necrosis/abscess. Numerous terms have been applied to the destructive process that accompanies necrotizing pancreatitis, including 'pancreatic abscess', 'pancreatic phlegmon', 'peripancreatic infection', 'peripancreatic sepsis', 'infected pancreatic collection' and 'infected pancreatic necrosis'. We favour Warshaw's classification[105]. a phlegmon is a solid mass of pancreas and adjacent retroperitoneal tissue caused by oedema, inflammation and/or tissue destruction but without bacterial contamination, whereas an abscess entails bacterial contamination, i.e infected pancreatic necrosis Pancreatic phlegmon is essentially a CT diagnosis, whereas pancreatic abscess produces a dramatic clinical picture.

If pseudocysts can be left to ripen, the development of a pancreatic abscess is generally an indication for prompt and radical surgery[125]. The incidence of pancreatic abscess, like that of pseudocyst, appears to reflect the aetiology of the pancreatitis: 39 per cent in postoperative pancreatitis, 15 per cent in traumatic pancreatitis, 7 per cent in alcoholic pancreatitis and 4 per cent in biliary pancreatitis[125]. The mortality rate of pancreatic abscess is substantial and correlates with Ranson's criteria of severity in acute pancreatitis, ranging from 14 per cent if there are 3 positive criteria to 100 per cent with 5 positive criteria[125]. Diagnostic laparotomy in the early stages of acute pancreatitis is said to increase the incidence of subsequent infection from 1.6 to 23 per cent in mild pancreatitis and from 24 to 67 per cent in severe pancreatitis[40]. The diagnosis of an abscess is suggested by hectic fever, abdominal pain, deteriorating health and leucocytosis. Pancreatic abscess is best confirmed by CT rather than ultrasound[20,21,97,104]. Percutaneous drainage is generally contraindicated in the management of pancreatic abscess, since the 'abscess' is basically an infected mass of necrotic peripancreatic tissue. However, recent evidence suggests that CT-guided fine needle aspiration of a pancreatic phlegmon or abscess for microbiological examination is both safe and reliable[126–128]. Moreover, percutaneous catheter drainage of loculated pus might avoid the need for repeat laparotomy in patients with a prolonged illness resulting from infected pancreatic necrosis. At laparotomy the entire retroperitoneum should be opened widely, with removal of necrotic fat and exploration of the pancreatic bed by the infracolic approach[125,129] The slough can extend forwards into the root of the mesentery and transverse colon, upwards to the diaphragm, laterally around the left kidney and downwards behind the descending colon, debridement should be tailored accordingly[130,131]. Haemostasis can be difficult, sepsis being exacerbated by coagulopathy, so fresh frozen plasma and platelets should be available for transfusions. Formal pancreatectomy is seldom feasible after the first few days of an attack of acute pancreatitis (see above), but necrotic pancreas can sometimes be removed piecemeal.

Following debridement a choice must be made between the closed and open techniques of abdominal management. For *closed drainage*, several wide-bore dependent drains should be placed to the abscess cavity at the end of the operation[132] We normally insert four silicone tube drains and commence postoperative lavage the following day, continuing with 50–100 ml saline per hour until the return effluent begins to run clear. Advocates of this technique report mortality rates for pancreatic abscess as low as 27 per cent[132] Perioperative hyperalimentation does not appear to alter outcome, providing malnutrition is not allowed to develop[133], but prolonged nasogastric suction does reduce the risk of death[125]

The alternative method, which is becoming more widely practised, is the technique of *laparostomy* or marsupialization[130,134,135], in which the abdomen is left open and evisceration is prevented by the use of moist packs. Most of these patients require ventilation, and the abdomen can be explored repeatedly in the intensive care unit under intravenous sedation, so that further collections are drained without recourse to formal operation. The proponents of this technique report a substantial improvement in mortality rate (14 per cent)[130] when compared to conventional drainage (75 per cent)[133,136] or suction drainage (13–55 per cent)[125,130,133] Although progressive sepsis and secondary haemorrhage are frequent sequelae[137], Bradley has treated 28 consecutive patients with infected pancreatic necrosis in this manner, using debridement, packing and scheduled re-exploration; the mortality was 11 per cent, and no patient died from sepsis[135].

Other complications Haemorrhage into the gastrointestinal tract may be due to concomitant peptic ulceration or gastro-oesophageal varices associated with splenic vein thrombosis or alcoholic cirrhosis. Inflammatory aneurysms of the splenic artery or other adjacent arteries may rupture and bleed, causing pancreatic apoplexy which is often fatal[138] Bleeding can be into the stomach or small bowel (after interval drainage of a pseudocyst, see above), into the peritoneal cavity or via drains to the exterior.

Most *pancreatic fistulas* result from external drainage of an abscess and will eventually close spontaneously[139]. Some recent success has been claimed for somatostatin and its analogues in reducing pancreatic secretion and expediting this process[140]. Should the fistula extend from the pancreas to other body compartments (particularly across the diaphragm into the mediastinum, pericardium and pleural space), then the outcome, in limited series, is better with surgical intervention than with conservative management[141].

Involvement of adjacent viscera may simply reflect obstruction of the distal common bile duct, stomach, duodenum or transverse colon by a large pseudocyst or abscess. Alternatively, these organs can undergo infarction if their blood supply is interrupted by extrapancreatic extension of the necrotizing process. Colonic necrosis and fistula formation usually follow drainage of a pancreatic abscess[142]. Recognition is difficult and prognosis is poor. Resection of the right colon is required with exteriorization of the lower bowel ending as an ileostomy and colonic mucous fistula[143,144]. Duodenal necrosis usually occurs on the medial wall adjacent to the papilla and is best managed by drainage[142]. Mural necrosis of the stomach requires local excision, and necrosis of the terminal bile duct is controlled by insertion of a T tube[145].

Conclusion

Overall, there has been little improvement in expected mortality and outcome for patients with acute pancreatitis since 1960[4,146]. There is no specific treatment of proven value other than energetic fluid replacement therapy An early attempt should be made to identify those patients with a bad prognosis using objective laboratory criteria and accepted scoring systems. This group of patients might well benefit from timely and appropriate operative intervention, which can be therapeutic (i.e. an early attempt to halt the progress of the disease) or in response to an established complication such as pseudocyst, abscess or bleeding. In a few cases of suspected acute pancreatitis diagnostic laparotomy is still needed. Prophylactic operations can prevent a further attack, mainly by prompt cholecystectomy but sometimes by draining an obstructed pancreatic duct.

Among these groups only therapeutic operations have yet to prove their value. Urgent sphincterotomy, whether operative or endoscopic, might prevent harmful progression of the pathological changes in the pancreas Total or subtotal pancreatectomy may salvage some moribund patients, but many othes are killed and there is a high complication rate. In neither case is it established that the benefits of urgent operation outweigh the substantial risks involved

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Review

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Modern aids to clinical decision-making in the acute abdomen

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Acute abdominal pain continues to provide not only a large workload for the general surgeon but also many diagnostic and management problems. Many different techniques have been introduced over the past two decades to help in the management of the acute abdomen and this review considers their relative claims to become incorporated into the process of clinical decision-making. The evidence in support of formally structured patient interview pathways with or without computer-aided diagnostic programs is now overwhelming and should become routine. Both laparoscopy and peritoneal cytology have an important role to play in the management of patients in whom the decision to operate is in doubt, and a combination of the two would be complementary. Ultrasonography has become increasingly popular for investigating the acute abdomen, and results from specialist centres are impressive. However, the problems of operator variation and the difficulties in providing a 24-h service will probably prevent it from becoming a first-line investigation in most hospitals. Although plain radiography has been available for many years, its routine use in the management of the acute abdomen remains controversial. Recent studies have confirmed that contrast radiography is an important adjunct to decision-making, particularly in the management of large bowel obstruction, and there is increasing evidence to support its use in suspected small bowel obstruction, perforated peptic ulcer and acute diverticular disease.

Keywords: Acute abdomen, decision making, differential diagnosis

Exploration of the peritoneal cavity first became feasible in 1846 following the discovery of anaesthetic agents by Morton in the USA (ether) and Simpson in the UK (chloroform). However, it was not until Lister introduced the principles of antisepsis 20 years later that there became a real possibility of survival after abdominal section. Although these events encouraged surgeons of the day to operate for large abdominal tumours, they remained hesitant to explore the acute abdomen Even the condition of acute appendicitis, then known as perityphlitis, was not fully understood until the latter years of the 19th century when, almost simultaneously, Samuel Fenwick of the London Hospital[1] and Reginal Fitz in the USA[2] recognized that early removal of the inflamed appendix could result in the cure of what had previously been an almost universally fatal condition

Following these and other reports, early exploration of the peritoneal cavity for acute abdominal pain gained in popularity and by the fourth decade of the 20th century Zachary Cope of St Mary's Hospital advised that abdominal exploration should even be extended to the doubtful cases when he wrote in his classic treatise on the acute abdomen in rhyme:[3]

> 'In doubtful cases do not wait too long,
> Before exploring for it is quite wrong,
> To act upon the slogan wait and see,
> When looking might provide the remedy '

Cope's approach was based on good clinical acumen and he stressed the importance of a detailed history followed by a meticulous examination[4]. Thus the concept of early operation to prevent the more serious complications of peritonitis was introduced, and even today most surgeons consider it to be both proper and correct to err on the side of an unnecessary operation rather than to miss a possible life-threatening condition amenable to surgery. Such a policy, however, is undoubtedly associated with unnecessary operations, a burden shouldered by patient, surgeon and health service alike On the other hand an effort to decrease the number of unnecessary interventions by a less aggressive operative approach may lead to some patients having an operation delayed· this has been termed in recent studies a 'bad management error'[5]. Traditional aids, such as urine microscopy, serum amylase and the presence of a pyrexia and leucocytosis, have played a central part in the clinical decision-making process for many years, but some – namely the presence of a pyrexia and leucocytosis – are of dubious value in the early management of the acute abdomen[6,7]. Serial white cell counts showing an upward trend can provide additional information in difficult cases of acute appendicitis (P. King and A A. Gunn, personal communication, 1989). The value of plain radiographs, except in circumstances where perforation or obstruction are suspected, have likewise been questioned[8], particularly when they are interpreted by a junior doctor[9]

Many new diagnostic and management aids have been introduced into the surgical decision-making process over the past decade or so to improve clinical performance This has been stimulated by the fact that in many instances the reliance

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on an exploratory laparotomy or indiscriminate period of observation and/or investigation is no more than a gamble, this is particularly so for the condition often referred to in common parlance as 'query appendicitis'. For example, figures well in excess of 25 per cent for the rate of removal of a normal appendix are not uncommon[10–13], despite continuing evidence that the complications which follow such an operation are not insignificant[10,14–16]. With the patients' welfare at stake and alternative aids available to improve clinical decision-making, the old adage that a certain percentage of normal appendices must be removed if one is not to miss an acute/perforated one[17] is no longer acceptable[11,16].

Assessment of performance

In the management of the acute abdomen, clinicians usually follow a well established pathway After an initial clinical assessment, which includes history, examination and the relevant emergency investigations, a provisional diagnosis is reached. Two decisions are then made: firstly to admit to hospital or to discharge; secondly, if admission is deemed appropriate, whether or not the patient needs an urgent operation. A recent study based within accident and emergency departments has shown that relatively high rates of clinical accuracy can be achieved by quite junior doctors with regard to deciding which patient requires admission to hospital[18] even though the diagnostic accuracy is less than 50 per cent[7,19]. Diagnostic accuracy is undoubtedly important, but surely is it not the accuracy of the clinical decision, irrespective of the diagnosis, which is of greater importance?[20] In other words, there are two pathways involved in the management of the acute abdomen. One aims at reaching a clinicopathological diagnosis from which a management strategy will follow, the other aims at reaching a procedural diagnosis (does the patient require operation or not?)[21]. Thus the assessment of any new diagnostic and management technique must take into account its ability to influence clinical decision-making (procedural diagnosis) rather than diagnostic accuracy (clinicopathological diagnosis) if a realistic and pragmatic appraisal is to be obtained[22,23].

Computer-aided diagnosis (CAD)

Over the past 15 years, both de Dombal[24–26] and Gunn[27] have pioneered the development of computer programs for the diagnosis of acute abdominal pain. They have used Bayes' theorem to calculate the probability of the presence of a condition given certain clinical findings. Clinicians enter the clinical data, collected on a structured data-sheet, into a computer-aided diagnosis (CAD) program. Diagnostic probabilities are then produced, using a large clinical database for reference. Thus both the clinician and the computer assimilate the same clinical data, the clinician using previous experience and acquired knowledge, and the computer using formalized Bayesian probabilities. These studies have demonstrated that the integration of CAD into clinical practice for the management of the acute abdomen results in a 20 per cent improvement in diagnostic accuracy[27] and that this improvement occurs across the board, from house officer through to consultant[25] Although early results of CAD produced an overall diagnostic accuracy in excess of 90 per cent[24], other studies, while confirming the improvement in diagnostic accuracy obtained from CAD, have so far been unable to reproduce this high figure[5,28,29]. This is perhaps because the original study[24] dealt with registrars only, whereas the later ones examined a cross-section of junior doctors[5]

In a recent multicentre study using CAD for acute abdominal pain[5], computers seemed to result in the following: an overall improvement in clinicians' diagnostic accuracy from 46 to 65 per cent; a reduction in the rate of 'negative' laparotomies; and a decrease in the number of 'bad management errors' from 0·9 to 0·2 per cent (this is the failure to operate on patients who are subsequently shown to have required surgery). In addition when CAD is used in the accident and emergency department there is an increase in the number of patients who are immediately discharged home without ill effects[19,27].

Other studies have successfully used CAD to help in the prediction of more specific diagnostic problems such as intestinal strangulation in cases of small bowel obstruction[30] and to differentiate an acutely inflamed appendix from a gangrenous or perforated one[31].

However, CAD has not been widely accepted[32] and has several disadvantages which include cost, the poor diagnosis of gynaecological problems, a high rate of diagnosis of non-specific abdominal pain[33] which reaches 50 per cent in some of the studies[24,29], and finally an inbuilt irrational resentment on the part of many clinicians to use computers in direct patient management, a resentment that might have quite deep-seated roots[34] There are certainly many obstacles to the acceptance of formalized clinical decision analysis[35]. Nevertheless, the improvement associated with the use of CAD cannot be ignored and has demonstrated not that the computer is cleverer than the clinician at diagnosing abdominal pain, but that it is better at accumulating and structuring the information gained by the clinician. Thus clinical acumen remains with the surgeon, and the familiar saying 'rubbish in, rubbish out' is particularly appropriate in this setting. The improvement with CAD is likely to be due to a variety of factors: a good clinical assessment which follows the use of a structured data pro forma; performance feedback with increased clinical awareness and peer/superior review; and an educational effect due to the direct comparison of the clinical diagnosis with that of the computer[36] An important factor is undoubtedly the use of a structured data-sheet which is required to accumulate the data for computer analysis. When these are used without the computer, diagnostic accuracy[27,37] and overall decision-making[21] can be significantly improved A similar improvement in performance is always likely when a clinical team focuses on the problem, especially when this is combined with regular feedback of results[5], peer review and audit[38,39] Thus the actual role of the computer itself in this overall improvement is difficult to quantify, and it is likely that it contributes less by itself than by association with the other factors already mentioned. This does not discount its central catalytic role[36].

In a recent trial comparing a Bayesian program against one based on rules[40], the latter appeared to be more popular (less unpopular) with clinicians. This type of system compares the clinician's diagnosis with that of the computer and then defines rules of play regarding the next line in management such as may be given over the telephone by a consultant to a registrar. So perhaps the idea of a computer helping the clinician is now less resented than was initially thought; this may be related to the increase in computerization in medicine in general, and amongst surgeons in particular[41,42].

Laparoscopy

Endoscopic examination of the human peritoneal cavity has been available in some form or other since the beginning of this century. Over the past 20 years it has been extensively developed, evaluated and finally adopted by gynaecologists[43]. The use of preoperative laparoscopy for acute abdominal pain is not new[44] and that it has a place in diagnostic decision-making in the acute abdomen has been strongly suggested by a number of studies, usually aimed at specific problems such as acute right iliac fossa or pelvic pain[45–49] Recent evidence has demonstrated that a selective policy of laparoscopy, used in patients with acute abdominal pain in whom the decision to operate is in doubt[22] significantly reduced management errors in this difficult group from 19 per cent to zero Those patients with 'query appendicitis' are particularly suitable for this technique as the normal appendix can be visualized at laparoscopy in at least three-quarters of patients[50], and with experience much more[51]. It can now be argued with some confidence that laparoscopy should be performed in all women with suspected appendicitis, irrespective of the certainty with which the diagnosis is made, because of the high error rate in this group[48,51–55] Failure to reduce unnecessary appendicectomy rates in spite of preoperative laparoscopy[56] may be the result of inexperience in the technique. Non-visualization of the appendix does not inevitably necessitate removal as signs of right iliac fossa inflammation will usually alert the laparoscopist to the possibility of appendicitis[48,49] Alternatively, another obvious cause may be found[51].

Laparoscopy is a safe procedure which is relatively simple to learn. A report[43] from the Royal College of Obstetricians and Gynaecologists gives a complication rate of around 3 per cent and a mortality rate of eight per 100 000 These figures include both diagnostic and operative laparoscopic procedures and contrast quite dramatically with the reported complication rate following the removal of a normal appendix, which ranges from 13 to 17 per cent[11,15] Admittedly, these results refer to laparoscopies performed on fit young women by experienced gynaecologists; the occasional laparoscopist in the surgical population may not fare so well If the widespread use of laparoscopy is to be advocated as an essential investigation in the management of the acute abdomen, general surgeons must first become expert laparoscopists For this to be achieved, laparoscopy must become more widely practised in all aspects of general surgery[57–63]. It must be remembered, however, that laparoscopy is an invasive technique and that not all patients are suitable Multiple previous abdominal operations and a provisional diagnosis of intestinal obstruction should be considered as relative contraindications, as is the presence of a large hiatus hernia or severe cardiopulmonary disease[64], conditions in which the production of a pneumoperitoneum is particularly hazardous.

Peritoneal cytology

Following the demonstration that cytological examination of a peritoneal aspirate and measurement of the percentage of polymorphonuclear cells could predict the need for operation in acute intra-abdominal inflammatory conditions[65], this technique has been used to improve clinical decision-making in the management of difficult cases of acute abdominal pain[66] When used in every patient with acute abdominal pain it also results in a significant reduction in inappropriate management decisions[67] This test, however, does not differentiate between acute inflammatory conditions requiring surgery and those that do not, although it does reveal those patients with a 'benign abdomen'. Thus it is likely to be of most value as a prelaparoscopy investigation, with negative results preventing unnecessary laparoscopies, and positive results indicating the need to proceed to either laparotomy or laparoscopy depending on the clinical pictures[68]

The technique of peritoneal aspiration cytology is relatively simple and can be performed under local anaesthesia on the ward or in the accident and emergency department[66,67]. After the bladder has been emptied, a size 14 G cannula is inserted into the peritoneal cavity midway between the umbilicus and pubic symphysis. A fine catheter – an umbilical one will do – with multiple fenestrations is passed through the cannula and suction is applied with a 10 ml syringe The aspirate is deposited on a slide and a thin smear is made and stained by the modified Romanovsky method; the cell profile is examined by microscopy and the percentage of neutrophils is counted. The risk of perforating underlying viscera is real, but appears to be of little consequence when a needle of this size is used[66].

Peritoneal lavage, although more familiar to surgeons for the investigation of blunt abdominal trauma[69], has also been used in the assessment of the acute (non-traumatic) abdomen with encouraging results[70]. Although this was stimulated by simple four quadrant tap[71] and then by a non-quantitative lavage[72,73], it has also been used in a quantitative fashion measuring peritoneal exudate volume by dye dilution[74] and intraperitoneal red and white cell counts[75,76] Although some authors have found biochemical analysis of the lavage effluent for amylase content to be neither reliable nor specific for diagnosing acute pancreatitis[72], others suggest that it may be of help in difficult cases[70]. However, the simplicity of the fine catheter peritoneal aspiration cytology technique, together with the objective result of neutrophil percentage, which corresponds well with the need for surgery, makes this procedure more preferable than lavage for investigating acute abdominal pain.

Ultrasonography

Ultrasound scanning has been used for many years in the diagnosis of hepatobiliary problems and is particularly useful for the detection of gallstones[77]. Recent advances in technology associated with real time scanning have allowed better images to be obtained and ultrasonography is now almost as accurate as scintigraphy in the detection of acute cholecystitis[78–80]. If a policy of early cholecystectomy is to be followed[81,82] then this form of investigation is invaluable in a hospital which cannot boast the possession of a nuclear medicine or clinical physics department A recent study has confirmed that an accurate decision to operate on patients with acute biliary symptoms can be based on clinical assessment and ultrasonography alone, with ^{99m}Tm hydroxyiminodiacetic acid scanning being reserved for difficult cases, where it still has an important role to play[83].

These improvements in ultrasonography have been associated with an increasing awareness by radiologists of the advantages of supplying a quick and non-invasive diagnosis to the patient with acute abdominal pain. Such is the enthusiasm in some departments that radiologists will happily perform ultrasonography for any acute abdomen at the surgeon's request[84] – and sometimes without it. A study reported recently from the Netherlands[85], using small high resolution linear-array transducers, has shown that acute appendicitis can be detected with a sensitivity of 75 per cent and, more importantly, with a specificity of 100 per cent. It would appear, however, that ultrasonography is not superior to clinical assessment in 'typical' cases of appendicitis, and its main use is in those patients with a doubtful clinical picture[86]. However, the practicalities of performing ultrasonography 'around the clock' and the problems of interobserver variation and experience[10,87] are the two main reasons that will probably prevent it becoming a routine investigation for 'query appendicitis'[88]

This problem has been addressed to some degree by a group of surgeons from Liverpool who trained their junior staff to use ultrasonography. After a surprisingly short (6 weeks) training period, surgeons reached a level of diagnostic accuracy of 92 per cent compared with the radiologists' figure of 96 per cent The authors estimated that clinical decisions were influenced in more than one-third of examinations, but admitted that 80 per cent of conditions scanned were hepatobiliary Unfortunately they made no attempt to scan patients with suspected appendicitis. There is also a possible advantage for high resolution ultrasonography in women with lower abdominal pain when the pelvic organs can be well visualized[87].

Thermography and white cell scanning

The introduction of a microwave thermography system which can detect intra-abdominal inflammatory foci[90] raises the possibility of using a combination of ultrasonography and thermography for the investigation of all patients with acute abdominal pain in whom the diagnosis or management decision is in doubt. Although radiolabelled white cell scanning can accurately identify intra-abdominal abscesses[91], at least 12–24 h are required for adequate imaging, and this limits its role in the 'acute' situation.

Plain and contrast radiography

Plain abdominal radiography has been advocated as a routine investigation for all patients with abdominal pain[92]. However, this view has been challenged[93,94] and other studies have suggested that its use be limited as it contributed to management in only 4 per cent of cases[95], even though valuable information was present in 66 per cent of films. The erect abdominal film for diagnosis of bowel obstruction has also been criticized[9,96], but the place of the erect chest film for the diagnosis of a pneumoperitoneum[97] still appears to be of value[8]. Junior staff are less likely to detect abnormalities compared with senior staff[92,96]; perhaps the message is not to restrict the types of emergency radiography available to junior staff, but to educate them better in their selection of patients[98] and in interpretation[99].

The use of contrast radiography in the acute situation is also controversial and, probably for that reason, underused The assessment of intestinal motility using contrast material is not new[100] and has been shown to be of value in the evaluation of patients with postoperative ileus[100,101]. More recently contrast radiographs, usually with water-soluble material, have been used to evaluate patients with suspected obstruction or perforation[102]. A recent study from Hong Kong[103] has shown that over 70 per cent of patients with a perforated peptic ulcer can be successfully managed non-operatively using an aggressive regimen of nasogastric suction, intravenous antibiotics and H_2-antagonists. Early identification of non-responders (those in whom spontaneous sealing of the perforation does not occur) can be made on the basis of a gastroduodenogram[104]. Likewise, contrast enemas have been used in patients with acute diverticular disease to identify those with a leak or 'peridiverticulitis'[105]. Thirteen of 16 patients with an identified leak/peridiverticulitis on contrast enema required surgery compared with only three of 30 patients in whom uncomplicated diverticular disease was seen.

There is now little doubt that a water-soluble contrast enema has an important role to play in the diagnosis and management of patients with large bowel obstruction[106,107]. It accurately identifies those patients with a mechanical cause for the obstruction, and who therefore require surgery, from those with pseudo-obstruction who, by definition, do not The use of prograde contrast studies for the investigation of small bowel obstruction has, however, achieved less acceptance among both surgical and radiological staff in the UK. Several studies have suggested that this form of investigation can be useful[108,109], but its influence on clinical decision-making has yet to be formally studied.

Discussion

The quest for improvement in the management of patients with acute abdominal pain has been stimulated by many factors, amongst which are an increasing public awareness – and indeed criticism – of the management of medical and surgical conditions; our unwillingness to accept some of the high error rates obtained in the past, and, perhaps most important of all, an innate desire to improve overall surgical management. The latter has been brought about by the ongoing audit and critical analysis that is now evident within the surgical specialities[38,39,110].

Further developments in the management of the acute abdomen will rely on sequential studies based upon historical controls. It is inappropriate that every new technique with which there are *a priori* grounds to disbelieve the null hypothesis should be subjected to a controlled randomized clinical trial when 'scenario' study technique, which assesses influence on clinical decision-making, is available[111]. The scenario method studies the influence of a new modality on patient management by comparing the error rate of the clinical decision before and after the technique has been applied. Such a method has been used successfully to evaluate the role of both laparoscopy[22] and peritoneal cytology[66] in the management of the acute abdomen.

There is now sufficient evidence to support the introduction of structured data-sheets in the initial history-taking and physical examination of the patient with acute abdominal pain, and these should become routine Next, clinicians can seek help from Bayesian reasoning undertaken by the computer to give an order of probabilities (and shortly it is hoped from rule-based programs) but even if they choose not to do this, they should be prepared selectively to use the new methods of investigation now available. For most patients with lower abdominal pain, these investigations will be peritoneal cytology and high resolution ultrasonography, when available, followed in a small proportion by laparoscopy. Further help can be obtained from contrast radiography, and it could be argued that those who are not pursuing routines of this kind are failing to deliver an adequate service to the patient with acute abdominal pain. All investigations, however, should be interpreted in the light of the clinical condition of the patient and surgeons must still be prepared to accept the occasional error in their pursuit of excellence.

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Acute haemorrhage from gastric malignancy

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The presentation, pathology and treatment of 30 patients with acute bleeding from gastric malignancies has been reviewed. Patients usually have a history of symptoms of less than 6 months prior to bleeding. Adenocarcinoma was the commonest type of tumour, and 74 per cent were stage IV lesions. The proportion of lesions in the body of the stomach (57 per cent) was greater than expected, suggesting that these are different populations of gastric tumour. Laparotomy was undertaken in 20 patients, 12 of whom had a resection. Resection was associated with a median survival of 17·0 months. Those with unresectable tumours or who were treated only by supportive measures had a median survival of only 2·5 months ($P<0·01$). Evidence of peritoneal or liver involvement should contraindicate surgical intervention as these patients have a high postoperative mortality rate.

Keywords: Gastric malignancy, acute haemorrhage

Although anaemia due to occult bleeding is a common presentation of gastric cancer, overt haemorrhage is less frequent, occurring in approximately 8 per cent of all cases[1,2]. Few reports have documented the natural history of gastric malignancy with such a presentation. In a review of 11 000 cases of gastric cancer, acutely bleeding tumours were associated with low rates of resection[3], reflecting extensive local growth before the development of symptoms.

In this study we have reviewed all cases of gastric malignancy admitted to the General Hospital, Birmingham, with acute bleeding in the period 1980–87 to determine the pattern of disease at presentation, to assess the prognosis, and to evaluate the various treatment options.

Patients and methods

Between October 1980 and August 1987, 1105 patients were admitted acutely with upper gastrointestinal bleeding (*Table 1*). They were managed in a designated gastrointestinal unit by a combined medical and surgical team. After appropriate resuscitation, endoscopy was performed, usually within 12 h of admission[4].

In suspected cases of gastric cancer, lesions were brushed for cytological examination and biopsied for histological examination Subsequent management was determined by the admitting physician. Further investigation and referral for surgery was therefore at the discretion of the admitting team and a standard protocol was not followed.

All patients with confirmed gastric malignancy have been reviewed and the clinical and pathological features, treatment and survival have been recorded Differences in survival were analysed using the Wilcoxon non-parametric test

Results

Clinical features

Thirty patients (20 men, 10 women; median age 72 years, range 49–91 years) had malignant lesions of the stomach. Presenting symptoms were usually those of advanced disease (epigastric pain and weight loss) but patients with a history longer than 6 months (eight patients) all complained of persistent dyspepsia, either alone or in combination with other symptoms. Those who underwent resection had a median duration of symptoms of 6 months (range 0–48 months) compared with 1·5 months (range 0–18 months) for those who did not undergo resection (not significant).

Endoscopic features associated with a high risk of rebleeding were not seen, and the lesions had superficial areas of haemorrhage without specific, identifiable vessels Seventeen (57 per cent) patients had tumours of the body, seven (23 per cent) had tumours of the antrum, five (17 per cent) had tumours of the cardia, and one (3 per cent) patient had tumour throughout the stomach.

Pathological features

Histologically, 27 of the lesions were adenocarcinomas. There were two lymphomas and one leiomyosarcoma. The stage of 27 adenocarcinomas was assessed from the operative and pathological findings or from the clinical and investigative results in those not undergoing surgery. The presence of hepatic metastasis was presumed in those with abnormal liver function tests and/or abnormal ultrasound examinations. Twenty (74 per cent) of the adenocarcinomas were stage IV, of which 12 were not resected (stage IVB, *Table 2*).

The two patients with lymphoma underwent laparotomy and, although both had extensive nodal and extranodal disease, one had resectable disease. The patient with a leiomyosarcoma of the pylorus/duodenum was declared inoperable because of local infiltration on ultrasound examination which was confirmed at autopsy.

At examination of the 12 resected specimens, eight were ulcerating lesions (Borrmann type 3), one was a flat infiltrating tumour (Borrmann type 4) and two were early cancers (early gastric cancer type I, polypoidal, and type IIb, flattened). The additional lesion was an ulcerating non-Hodgkin's lymphoma. In only two of the lesions were there haemorrhagic areas associated with the main tumour

Treatment

Laparotomy was performed in 20 patients, 12 of whom underwent resection. In no case was surgery performed as an

Table 1 *Cause of upper gastrointestinal bleeding in 1105 patients*

Diagnosis	No. of patients ($n=1105$)
Oesophagitis	100 (9·1)
Mallory–Weiss syndrome	55 (5·0)
Oesophageal varices	70 (6·3)
Gastric ulcer	207 (18·7)
Gastric malignancy	30 (2·7)
Duodenal ulcer	382 (34·6)
Extragastric malignancy	18 (1·6)
Others	138 (12·5)
None	105 (9·5)

Values in parentheses are percentages

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Table 2 *Clinicopathological stage of 27 gastric adenocarcinomas giving rise to bleeding* (*after Fielding* et al.[5])

Stage	No
I (Serosa negative, node negative)	1
II (Serosa positive, node negative)	0
III (Serosa positive, node positive)	2
IVA (Reaction, gross residual disease)	8
IVB (No resection, gross disease)	12
Not known	4

emergency for continued bleeding, operation usually being performed in the first 5 days after admission. Resection was considered curative in three patients (stage I, one patient; stage III, two patients) and palliative in nine patients, two of whom had macroscopic residual nodal disease and seven of whom had microscopic involvement of the proximal resection margin. The remaining eight patients did not undergo resection because of previously undiagnosed liver metastases (two cases), extensive local invasion (three cases) or both (three cases).

The reasons for non-surgical management were as follows: three patients were not considered fit for operation, two had extensive local disease, and five had either liver metastases (four patients) or peritoneal spread (one patient). These patients were significantly older (mean age 77·4 years) than those who had a resection (mean age 65·2 years) ($P<0.01$) and those who underwent laparotomy alone (mean age 66·6 years) ($P<0.01$). Patients who were managed conservatively received symptomatic measures only. None suffered further acute bleeding.

Survival

The overall median survival was 9 months. Seven patients (23 per cent) died within 30 days of admission, including four who underwent laparotomy alone (*Figure 1*). There was no operative mortality for those undergoing resection. The median survival following resection was 17·0 months which contrasts with 2·5 months for those with unresected tumours ($P<0.01$).

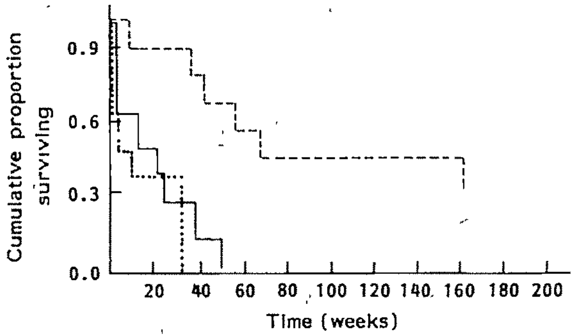
Patients undergoing laparotomy only had a similar overall survival to those treated conservatively (*Figure 1*). However, if patients who presented in the terminal phase and died soon after admission are excluded, those treated conservatively survived for a significantly longer period (median survival 5·0 months compared with 1·5 months, $P<0.05$).

Discussion

The proportion of patients presenting with upper gastrointestinal haemorrhage who were found to be bleeding from gastric malignancies (2·7 per cent) is similar to that recorded by others. Schiller and colleagues[6] identified 47 cases of gastric cancer (2·2 per cent) in 2149 emergency admissions with haematemesis and melaena. In that series 34 per cent of the patients with malignancy died in hospital compared with 23 per cent in the present study.

The high hospital mortality rate was largely due to the fact that over 70 per cent of the patients had stage IV disease at presentation, i.e. disseminated malignancy (liver or peritoneal secondaries) or local malignant infiltration to adjacent structures, which was amenable at best to palliative resection. The proportion with stage IV disease was, however, no higher than that observed in all patients with gastric cancer: in a large population-based series from our region, approximately 80 per cent of those with gastric cancer had stage IV disease at presentation[7].

Walters and colleagues[3] have suggested that gastric cancers which bleed acutely may represent a different population, developing insidiously with either no symptoms or relatively minor symptoms. By the time of symptomatic presentation the underlying lesions are too advanced for radical surgical ablation. This study concurs with this hypothesis as most tumours were in the body of the stomach and these cause less characteristic symptoms than cardia or antral lesions. Furthermore, tumours of the body account for 19 per cent of all gastric cancers[7], as opposed to the proportion of 57 per cent observed in this study.



Numbers at risk

Resection	12	9	7	6	4	4	3	3	3	2	1
Laparotomy only	8	2	0								
No operation	10	4	2	0							

Figure 1 *Monthly survival by life-table analysis of 30 patients with gastric malignancy.* ----, *Resection,* ······, *laparotomy only,* ——, *no treatment*

Such a difference in the pattern of presentation implies a different approach to management. In common with other presentations of gastric cancer, resection must be the treatment of choice. In the present series, patients undergoing resection had a longer median survival than those who did not, despite the fact that 75 per cent had only a palliative procedure. However, the selection of patients with lesions suitable for resection remains a difficult problem. After initial resuscitation, none of the patients in this series required an emergency operation to control bleeding. Thus time was available for adequate assessment and confirmation of the tissue diagnosis. Non-operative management in the presence of disseminated disease was associated with a modest period of survival, although a subgroup of patients who were in the terminal phase of their illness died quickly. By contrast, laparotomy in an apparently fitter group with equivalent spread of disease had a high operative mortality rate and a correspondingly shorter prognosis. Thus, only in those patients without liver metastases or disseminated disease should laparotomy with intent to resect be undertaken. Although preoperative staging of gastric cancer is limited[8] patients should be assessed by ultrasound or computed tomographic scanning. Such a policy would prevent those with a very short prognosis from spending a large proportion of that time recovering from an unnecessary laparotomy.

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Technique and preliminary results of extracorporeal liver surgery (bench procedure) and of surgery on the *in situ* perfused liver

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The clinical experience with 11 patients undergoing ex situ *operation of the liver (nine operations) or surgery on an* in situ *hypothermic perfused liver after vascular isolation (three operations) is described. These methods have been confined to situations and tumour stages otherwise deemed untreatable, or to situations where resection would not have been sufficiently radical. In one patient the* ex situ *approach avoided the need to undertake liver grafting for a benign tumour. To date, hepatocellular tumours and metastases not compromising global hepatic function or causing cholestasis are considered to be suitable conditions; cholestasis appears to be highly detrimental for the postoperative course after an* ex situ *procedure. Elaboration of methods for better grading of pre-existing liver damage and of its prognostic significance is essential. The assessment of the final therapeutic value of the described procedure requires further experience.*

Keywords: Extracorporeal surgery, *in situ* hypothermia, liver resection

Extracorporeal surgery on the kidney has become a standard procedure for difficult arterial reconstructions[1] and for resection of some malignant renal tumours, particularly those arising in a solitary kidney[2] Both tumour radicality and surgical precision can be enhanced by this procedure, compared with the conventional *in situ* approach. Experience and advances in hepatic transplantation have opened the possibility of bench surgery for liver disease[3]. We performed the first *ex situ* operation on the liver in February 1988 on a 46-year-old patient to remove huge metastases from a leiomyosarcoma of the stomach, which otherwise had been assessed as truly unresectable[4]. The surgical procedure and the postoperative course of this patient was uneventful. Since that time we have operated on eight other patients using the same procedure, and in three patients we have reintroduced *in situ* hypothermic perfusion after vascular isolation, so as to operate on a bloodless liver without pressure of time. The principles of this approach were developed by Fortner *et al.*[5] in 1974. In this paper the techniques of both approaches and the course of the patients treated so far are described, and the prospects and hazards are discussed

Technical considerations

The ex situ *approach*

The principles used were those of liver grafting, with the following variations.

In liver transplantation, grafts are harvested with long vessels, preferably with an aortic patch, in contrast to the *ex situ* procedure where long vessels or patches are not available Thus meticulous dissection and reanastomosis of vessels is mandatory. It seems advisable to dissect the suprahepatic vena cava from the diaphragm in case extrapericardial or intrapericardial clamping is needed, and to facilitate reanastomosis. However, this procedure was not performed in every case Caval branches, particularly the right suprarenal vein, were dissected and ligated carefully Hilar neural and lymphatic tissue was removed in most instances in a radical way, the common bile duct was isolated by dissection of its middle segment, except in cases of central bile duct tumour, where the common bile duct was dissected as close as possible to the duodenum

As anhepatic periods always last for several hours, bypass is mandatory Venovenous bypass from portal vein and inferior vena cava to the axillary vein using heparin-bonded Gott® shunts and biopump[6] was performed in all instances The use of a heat exchanger protected against severe hypothermia. During insertion of the bypass and interruption of portal perfusion, the arterial blood supply to the liver was maintained. Careful anaesthetic management is essential to compensate for changes during the anhepatic phase[7]

Hypothermic liver perfusion was commenced *in situ* after clamping of the suprahepatic and subhepatic vena cava and dissection above the subhepatic clamp. The liver was able to be removed within 1–2 min, given the previous vascular isolation; extracorporeal perfusion then seems acceptable and more reasonable since the liver can be placed simultaneously in iced water, thus avoiding cooling of the patient. Care was taken to dissect the suprahepatic caval vein for at least some millimetres above the hepatic vein confluence Perfusion was performed in all instances with the cardioplegic solution, HTK (Bretschneider)[8,9], initially with 6 litres intraportally and 0 5 litres intra-arterially Perfusion was repeated at intervals of 1 hour with 1 litre and 0 2 litres, respectively.

Ex situ *surgical procedures on the liver*

Surgical manoeuvres on the extracorporeal liver have to be adapted to the individual findings and are not described in detail. In principle, dissection begins on structures which must be preserved and might be harmed by conventional resection. Small arterial branches or essential liver veins must be preserved Of course, main liver veins including the cava itself can be resected over a limited length and reconstructed or reinserted using the *ex situ* technique This seems critical for smaller intrahepatic arterial branches Vascular interruption must be carefully avoided in areas of liver which have to be preserved The fatal outcome in one patient (see *Table 1*, patient no 7a) was mainly due to such an error. After freeing the essential structures to be preserved, liver resection can be performed in the manner used for conventional liver resection, ligating structures that cross the resection line or clamping them with haemoclips Resection lines follow the segmental structure of the liver[10] The advantage of the *ex situ* technique is that segmental lines may be extended, for example by resecting directly along a main vein when segmental 'borderlines' are not precisely definable. After completion of resection, unligated and open vessels or bile ducts can be identified by perfusing the individual system Open large vessels should be oversewn or ligated to avoid severe bleeding after reimplantation. Complete closure of all small leaks, particularly small holes along larger veins, is achieved by covering the resection surface with fibrin glue Any vascular reconstruction required for reanastomosis should be done *ex situ*

Reanastomosis is usually carried out in the normal sequence. suprahepatic vena cava, subhepatic vena cava (with a catheter inserted to allow perfusate to be flushed out of the liver), hepatic artery and portal vein If the arterial, or exceptionally the portal, anastomosis requires considerable time, reperfusion may commence using one of the systems in order to avoid a prolonged rewarming period

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Table 1 *Operations and follow-up data after* ex situ *operation on the liver in nine patients*

Patient no.	Age (years)	Diagnosis	Indication group*	Operation	Operation time† (h)	Intraoperative complications	Maximum ischaemic damage SGOT (units/litre)	Maximum ischaemic damage GLDH (units/litre)	Postoperative follow-up
1a	40	Metastasis from leiomyosarcoma Extrahepatic metastasis	III	Segmental resection (II, III, V, VI, VII, VIII) (4·5 kg) Reimplantation of segments I and IV	16 (6)	Bleeding	740	560	Uneventful Good palliation Discharged after 8 weeks
2a	46	Multiple metastases (colonic carcinoma)	III	Segmental resection (V, VI, wedge VII)	15 (5)	None	450	40	Uneventful ?Palliation Discharged after 2 weeks
3a	52	Klatskin tumour Recurrent cholangitis	III	Right extended hemihepatectomy (trisegmentectomy) Partial resection and reconstruction of inferior vena cava	12 (4)	None	19	180	Reduced liver function during 2 weeks Discharged after 4 weeks
4a	58	Metastasis of colonic carcinoma Infiltration of vena cava Cholestasis Post non-A, non-B hepatitis	III	Right extended hemihepatectomy (trisegmentectomy) Reconstruction of inferior vena cava	11 (7)	Delayed reperfusion	27	250	Hepatic insufficiency Sepsis Died after 44 days
5a	30	Huge focal nodular hyperplasia in segment IV Compression of inferior vena cava	II	Segmental resection (I, IV)	11 (4)	None	80	60	Uneventful Discharged after 2 weeks
6a	57	Sigmoid carcinoma Infiltration of right hepatic vein	III	Left extended hemihepatectomy (2 kg)	11 (6)	None	678	1150	Delayed recovery Discharged after 8 weeks
7a	48	Klatskin tumour with extrahepatic metastasis Cholestasis	III	Left extended hemihepatectomy Gastrectomy Pancreatectomy, splenectomy Reconstruction of hepatic artery (saphenous vein interposition)	16 (6)	Delayed reperfusion of segment V	792	1243	Hepatic insufficiency, transplantation, sepsis, multiple organ failure Died after 50 days
8a	62	Klatskin tumour with infiltration of left and right portal vein Cholestasis	II	Hilar resection Reconstruction of portal vein	18 (9)	Bad reperfusion oedema	984	362	Hepatic insufficiency, transplantation after 22 h Remains in critical condition
9a	54	Klatskin tumour with moderate cholestasis	II	Right extended hemihepatectomy (trisegmentectomy) Reconstruction of hepatic artery and portal vein	13 (4)	Delayed reperfusion	770	1000	Deterioration of liver function on 3rd day, requiring liver transplantation on the 17th postoperative day Retransplantation 2 days later (initial non-functioning organ) Sepsis, multiple organ failure Died on 23rd day

* See *Table 3*; † values in parentheses show the length of the anhepatic phase of the operation, SGOT, serum glutamic oxaloacetic transaminase, GLDH, glutamic lactate dehydrogenase

Finally, reconstruction of the biliary system is carried out according to the individual situation, either by an end-to-end anastomosis of the common bile duct or by anastomosing the common bile duct or the intrahepatic bile ducts to a Roux-en-Y loop of jejunum

Vascular isolation and in situ *hypothermic perfusion*

Isolation of the liver includes complete dissection of the posterior wall of the retrohepatic caval vein Dissection of the suprahepatic vena cava from the diaphragm is not necessary In two patients the standard extracorporeal bypass procedure was used as described above. in one case the portal system was drained via the inferior mesenteric vein[11], and in the other by dissecting the portal vein In the third patient an intracaval shunt was applied, but was ineffective owing to problems in fixation Since cross-clamping of both the portal vein and the inferior caval vein was well tolerated, hypothermic perfusion of the liver and resection were performed without bypass.

Hypothermic perfusion with HTK–Bretschneider solution was always accomplished after incision or transection of the portal vein. The arterial system was simply clamped, and was not perfused. The liver was wrapped in silver foil to prevent rewarming of its surface. Resection was carried out according to the individual findings; the ischaemic situation allowed particularly difficult resections in the areas surrounding the large liver veins

Patients

Details of the 11 patients treated between February 1988 and February 1989 by these approaches are recorded in *Tables 1* and 2.

Ex situ *operations*

Patient 1a. Owing to previously resected peritoneal metastases, liver grafting was contraindicated. Tumour growth of the leiomyosarcoma was, however, slow and the huge liver masses (*Figure 1*) gave rise to severe symptoms, so that surgical intervention was indicated. *In situ* hypothermic perfusion and vascular isolation was originally planned but was found to be impracticable due to tumour size. Since liver function was normal, the first *ex situ* operation was undertaken. Although only segments I and IV (approximately) could be preserved after removal of the 4·5 kg tumour and surrounding liver tissue, postoperative liver function was good and the course was uncomplicated The patient had to undergo further resection of metastatic tumour adjacent to the stump of the stomach 6 months later, she remains well without further evidence of tumour recurrence

Patient 2a (*also 2b in Table* 2) After ineffective chemotherapy, multiple liver metastases from a colonic tumour were dealt with in this young patient by the new approach. Preoperative liver function tests were normal, and the postoperative course was uncomplicated The operation showed that the *ex situ* technique allows proper radicality regarding tumour-free margins in segmental resection as well as in extended wedge resections Distribution of metastases in all segments (not seen in ultrasonography or computed tomographic scan before operation) led us to monitor the patient for early tumour recurrence This occurred 3 months later but the metastasis appeared to be superficial and thus another operation was indicated During this operation, *in situ* hypothermic perfusion was used (see patient 2b) It should be stressed that we regard this procedure as extraordinary and it was undertaken only following pressure from the patient and her family for us to attempt such an extreme surgical procedure

Patient 3a. Tumour infiltration of hilar lymph nodes from the Klatskin tumour was seen as a contraindication to hepatic transplantation, deep tumour infiltration of the liver parenchyma and retrohepatic caval vein excluded a conventional resection Preoperative biochemical tests showed evidence of cholestasis, but liver synthesis tests were normal. After operation serum bilirubin levels increased and remained elevated for prolonged periods, although liver function recovered after 3 weeks The patient remains well 10 months after operation

Patient 4a The indication was similar to that of case 3a A conventional right extended hemihepatectomy was planned and was begun by ligation of the right hepatic hilar stem vessels. However, infiltration of the confluence of the hepatic veins, the extent of which was not recognized before, rendered the situation untreatable by

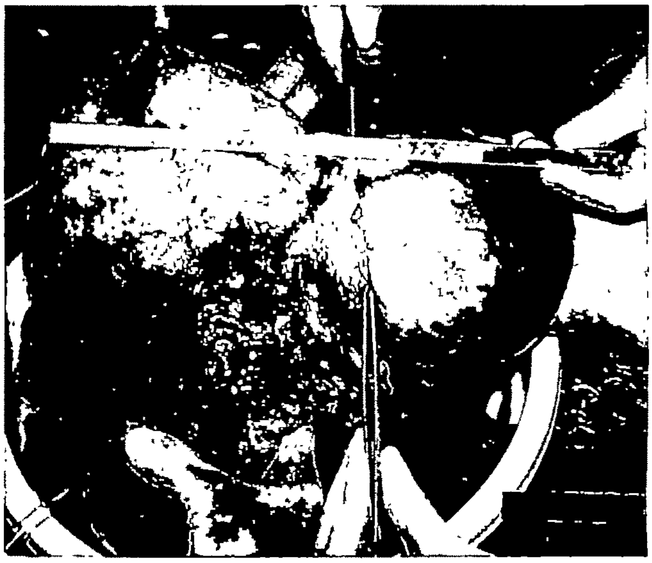

Figure 1 *Patient 1a two huge metastases of a leiomyosarcoma in the left and right lobe measuring 10 and 14 cm in diameter respectively were resected (tumour mass 4 5 kg) Segments I and IV (1 kg) were reimplanted*

Table 2 *Operations and follow-up data from three patients after operation on a liver with hypothermic perfusion and vascular isolation*

						Maximum ischaemic damage		
Patient no.	Age (years)	Diagnosis	Indication group*	Operation	Ischaemic time (min)	SGOT (units/litre)	GLDH (units/litre)	Postoperative follow-up
1b	55	Metastasis from colonic carcinoma with possible infiltration of the vena cava	III	Segmental resection (I, VII, VIII and right hepatic vein)	120	546	945	Uneventful Discharged after 2 weeks
2b	46	Multiple metastases from colonic carcinoma Infiltration of remaining right hepatic vein (post *ex situ* operation)	III	Subsegmental resection (VIII) Reimplantation of right hepatic vein	168	357	212	Uneventful Discharged after 10 days
3b	63	Hepatocellular carcinoma (I, V, VIII) Infiltration of right hepatic vein	II	Segmental resection (I, II, III, wedge V, VIII) Preservation of right hepatic vein	30	116	61	Uneventful Discharged after 4 weeks

*See *Table 3*, SGOT, serum glutamic oxaloacetic transaminase, GLDH, glutamic lactate dehydrogenase

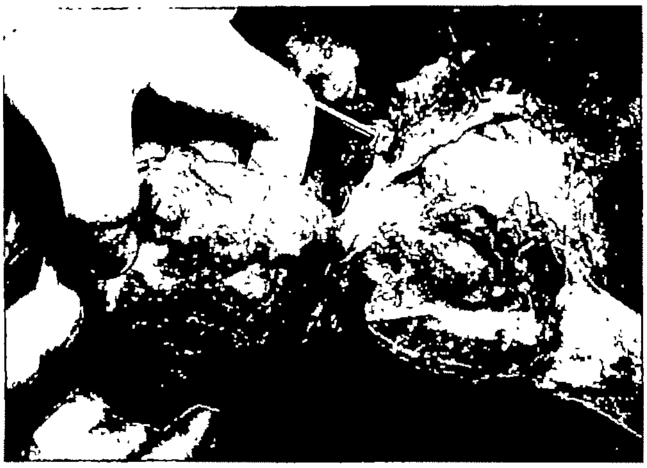

Figure 2 *Patient 5a: a huge lesion (focal nodular hyperplasia) localized in segments I and IV caused a compression of the inferior vena cava with recurrent orthostatic collapse. The focal nodular hyperplastic nodule was resected* ex situ *by dissecting the caval vein from the posterior surface of the liver*

conventional techniques. Thus, in spite of previous non-A non-B hepatitis and increased tenderness of the liver, an *ex situ* procedure was performed to try to save an otherwise hopeless situation. Technically, the resection of the tumour, including the confluence of the hepatic veins with reanastomosis of the left hepatic vein to a reconstructed cava, was feasible. However, during intensive care over the succeeding 44 days liver function deteriorated, resulting in death with multiple organ failure. Histology of the liver showed focal necrotic zones indicating septic hepatocellular injury.

Patient 5a. Focal nodular hyperplasia is not normally thought to be an indication for operation. However, in this young patient increasingly severe symptoms of inferior caval vein compression (including orthostatic collapse due to the location of the 7–8 cm nodule in the hepatic vein confluence) clearly indicated the need for surgical treatment. At laparotomy and after meticulous preparation it appeared that removal of the tumour in this critical area carried an unacceptable risk. An *ex situ* operation was not thought to be justified as this had not been discussed thoroughly with the patient Furthermore it was decided that for this particular situation a liver graft should be available in case the *ex situ* operation failed[12]. This reoperation was undertaken 2 weeks later when a donor organ was available. The *ex situ* approach turned out to be an ideal way of resecting this focal nodule as it was possible to dissect the caval vein from the posterior surface of the liver and thereby open the area between the main hepatic veins to allow removal of the tumour which compressed the venous system (*Figure 2*). The operation and the postoperative course were uncomplicated. (The 'reserved' liver graft was transplanted successfully into another patient 14 h later.)

Patient 6a. Infiltration of the vena cava near the hilar structures made resection by conventional methods impracticable Although preoperative liver tests were not normal, an *ex situ* operation was attempted. The tumour (a deposit from a sigmoid carcinoma) could be resected, preserving the right hepatic vein. The postoperative course of this patient was complicated by prolonged hyperbilirubinaemia and by exudate formation at the resection area, which was drained percutaneously. Although the patient was discharged 8 weeks after the operation, in retrospect the preoperative liver function was too poor to perform this procedure.

Patient 7a Infiltration of the bifurcation of the portal vein and of the parenchyma by a Klatskin tumour in combination with advanced tumour spread in parapancreatic and coeliac axis lymph nodes rendered conventional resection impracticable and liver grafting irrational. In view of the age of the patient (48 years) and an acceptable clinical situation with good liver function, complicated, however, by cholestasis, *ex situ* resection was chosen. The *ex situ* liver resection (left trisegmentectomy, reconstruction of hepatic artery by saphenous vein) was combined with resection of the total coeliac axis with pancreatectomy, gastrectomy and splenectomy. The residual liver tissue consisted approximately of segments VI and VII and of segment V However, the essential arterial branch to segment V had been resected with the tumour After revascularization with end-to-end anastomosis of the portal vein and an arterial reconstruction (via saphenous vein interposition from the right common iliac artery), segment V, although perfused, remained discoloured. Because of the small amount of remaining liver tissue, it was not resected. This turned out to be a major error. After a good initial recovery with acceptable liver function, the patient became septic. Reoperation showed infarction of segment V. In spite of removing as much necrotic tissue as possible by two further operations, liver function deteriorated. Hepatic transplantation was undertaken but the patient died 50 days later from further septic complications Retrospectively, it is assumed that the extended surgical procedure might have succeeded if the underperfused area of segment V had been resected during the first operation. Thus total removal of the coeliac axis with pancreatectomy, gastrectomy and *ex situ* hepatic surgery may still be justified in selected situations, as has been shown in combination with liver transplantation[13] or in combination with pancreatic and stomach transplantation[14].

Patient 8a. Significant cholestasis (bilirubin 400 μmol/l) and reduced liver function prompted the decision to attempt *ex situ* resection of a Klatskin tumour infiltrating both portal stem branches (thus avoiding extended liver resection which the patient was thought unlikely to tolerate). During the *ex situ* surgery all of the central bile ducts were found to be infiltrated, and therefore deep central parenchymal resection had to be carried out. Extensive vascular replacement of the portal branches and the arterial system then had to be performed. The difficult multiple hepaticojejunal anastomoses were carried out extracorporeally. After reanastomosis reperfusion of the liver was extremely poor and the liver felt stiff. Failure of the procedure was recognized and an emergency liver graft was planned As the haemodynamic situation of the patient deteriorated dramatically, hepatectomy with portacaval anastomosis was undertaken[15]. This stabilized the haemodynamic condition until a liver graft was available and inserted 10 h later The patient remained critically ill 80 days after liver grafting. Several indirect complications (for example, severe bleeding from the urinary bladder) contributed to the complicated postoperative course. Retrospectively, liver damage from cholestasis was probably too advanced for resection whether undertaken as an *ex situ* procedure or by conventional means.

Patient 9a. In spite of the failure in case 8a, *ex situ* resection for this patient's Klatskin tumour seemed justified. Hyperbilirubinaemia had been transient only, and liver function and the appearance of the liver during operation were normal. The left bile duct system appeared unaffected. A conventional right extended hepatectomy would have been achievable, but was thought to be potentially non-radical. In contrast, extracorporeal resection allowed a high degree of radicality with wide distances between resection lines and the tumour. The course of the operation was smooth (total blood loss substitution by two erythrocyte concentrates) and the rest of the liver (segments II and III) appeared to be well perfused. Vascular reconstruction consisted of reanastomosing the left portal stem end-to-end and providing an arterial supply from a saphenous vein interposition from the right common iliac artery (because of a preoperative diagnosis of stenosis of the coeliac axis) The first 2–3 days after operation were uneventful and the patient was extubated and awake. Unexpectedly, deterioration of liver function began on day 3 with high fluctuating serum transaminase levels (> 1000 units/l), and the onset of coma with critical liver function occurred during the next 10 days. Vascular complications had been excluded repeatedly by Doppler ultrasonography. Finally, on day 15, liver transplantation was deemed to be indicated, and was performed on day 17. The patient's own liver appeared swollen and fatty, the vascular supply being intact. The graft initially showed signs of non-function. A second graft was performed 2 days later but the patient succumbed to septic complications after 4 days.

In situ *operations with hypothermic perfusion and vascular isolation*

Patient 1b. After wedge excision of two liver metastases (from colonic cancer dealt with 1 year earlier) and ineffective chemotherapy, including hepatic arterial port implantation, resection of recurrent liver metastases was attempted To remove these nodules in segments I, VII and VIII, a vascular isolation and hypothermic perfusion technique seemed appropriate. Resection of these segments included the right hepatic vein, which was tolerated because of the presence of an additional smaller inferior right hepatic vein Bypass was not instituted, but was available

Patient 2b. This situation has already been explained (see patient 2a).

Table 3 *Groups of indications for* ex situ *liver surgery or* in situ *hypothermic preserved liver surgery*

Group	Possibilities for		Indication for *ex situ* technique/ *in situ* hypothermic technique
	Conventional resection	Hepatic transplantation	
1 Preferable	Possible	Not indicated	Aim: higher degree of tumour radicality?
2 Optional	Possibly applicable or presumably non-radical	Possible but perhaps avoidable or/ and burdened by bad prognosis	To improve radicality and to perform meticulous vascular repair
3 Necessary	Impossible	Contraindicated	Only chance for surgical resectional treatment

Patient 3b A hepatocellular carcinoma in the region of the hepatic vein confluence, and infiltration of the left and middle veins (and possibly also of the right vein), were the reasons for abandoning an attempt at conventional resection Another approach had not been discussed with this patient before operation. Recovery after the laparotomy was slow, and was complicated by fever Nevertheless after 4 weeks, and having discussed the possibilities with the patient thoroughly, a second approach was attempted. The reduced general health of the 63-year-old patient made an *in situ* resection preferable to an *ex situ* resection, particularly as the need for major reconstructive procedures was not expected In the *in situ* hypothermic, bloodless situation, an extended left hemihepatectomy including parts of segments V and VII was carried out, selectively preserving the right hepatic vein

All three patients who underwent *in situ* hypothermic perfusion had an uncomplicated postoperative course and are currently alive, although patient 2b has distant and liver metastases

Discussion

Liver surgery has reached a high standard in recent years with increasing numbers and extent of resections and a reduction in mortality rate[16–18]; this also applies to hepatic transplantation Thus it can be argued that non-conventional methods such as the *ex situ* approach or the *in situ* preserved liver surgery may not be necessary. Undoubtedly these approaches are necessary only in selected cases. In our institution during the 1-year period during which we performed the 12 unconventional operations reported here, 131 major conventional resections for malignant or benign tumours and 18 hepatic transplantations for malignancy were performed.

The new *ex situ* approach and the *in situ* procedure can be regarded as having the following aims: (a) to increase the resectability rate in patients with advanced tumours; (b) to improve the radicality of tumour resections; (c) to avoid the need for liver grafting, particularly in patients with tumours with generally unsatisfactory results and those with benign tumours, and (d) in theory, to allow oncological methods to be used extracorporeally.

In principle, there are three groups of indications for the unconventional new approaches (*Table 3*)· in introducing a new method, the group 1 indication (preferable) will not be justified, although in time it may have relevance; none of the patients in this report was in this indication group. Indications for group 2 (optional) and particularly for group 3 (necessary) are justified if there is at least a chance of improvement which otherwise would not be achieved. All of the first four patients treated with the *ex situ* approach, patients 6a, 7a, and patients 1b and 2b in whom the *in situ* approach was used, belong to this third indication group. In patients 5a, 8a and 3b, liver transplantation was an option, and in patient 9a a conventional resection would have been an alternative, thus placing these patients in indication group 2. With regard to the underlying disease and to the liver situation, all patients with hepatocellular diseases survived (patients 1a, 2a, 5a, 1b, 2b, 3b) except patient 4a. In this patient, who had a history of a non-A non-B hepatitis, the operation was done as an emergency. In contrast, all patients with bile duct disease had a complicated course (patient 3a) or treatment failure (patients 7a, 8a, 9a), and an attempt to salvage the outcome by liver grafting was always made. Failure in patient 7a was caused by sepsis, and in patient 8a it was already apparent during the operation; in contrast the failure in patient 9a was not at all expected. Thus it might be argued that cholestasis, even if clinically latent with moderately elevated biochemical tests, may cause significant damage to the liver parenchyma, which is aggravated markedly by other injuries such as hypothermia and cold ischaemia. If this assumption is correct, it has to be determined whether long-term drainage procedures can reduce the impact of cholestasis to a degree that might allow additional damage. It seems questionable whether this can be achieved by retrograde or transhepatic drainage, which are always prone to infective complications. We now prefer a double-sided hepatojejunostomy for palliation as well as for relief of severe jaundice before liver resection[19,20] but have not performed this operation in preparation for *ex situ* surgery.

Thus, initial experience suggests that the *ex situ* technique is particularly applicable to hepatocellular tumours or metastases in patients who do not have seriously impaired liver function or impaired bile secretion. Although we will continue to use these techniques in patients in indication groups 2 and 3, it now seems reasonable to begin to discuss group 1 indications in selected situations.

Regarding the choice between an *ex situ* procedure and an *in situ* hypothermic approach, the following preliminary assessment may be made in situations requiring specific reconstructions in the area of the confluence of the hepatic veins and inferior vena cava the *ex situ* approach seems to be indicated Technically, the *ex situ* approach would also be suitable for Klatskin tumours and for other hilar operations. Resections in regions where preservation of an essential hepatic vein is critical (for example, the need to resect two and preserve one main liver vein to which the tumour might be adjacent), as well as atypical resections in the depth of the liver, may be indications for *in situ* hypothermic perfusion. The choice between normothermic vascular isolation[21] and hypothermic perfusion with vascular isolation may be made individually

For preservation of the liver, the HTK–Bretschneider solution, primarily developed for cardioplegia, has been used following experimental studies on the liver and on kidneys[22,23]. The solution contains a potent histidine buffer which is of particular interest in moderate hypothermia. Thus, partial or repeated rewarming of the liver, which cannot be avoided completely in the *ex situ* and particularly in the *in situ* approach, may be less harmful. In contrast to all other preservation solutions actually available, the HTK–Bretschneider solution has a low potassium content (10 μmol/l) which minimizes the risk of cardiac arrest during reperfusion. Our group has experience to date with the solution for clinical liver grafting in 14 patients; it is our impression that the solution offers useful preservation[24].

A further aspect of the *in situ* hypothermic perfusion technique is its use in obtaining a partial liver graft from a living related donor. Separation of segments II and III, which would be the preferred part of the liver for such a procedure, may also be performed in the normothermic, blood-perfused situation. However, the hypothermic status may be less harmful to liver performance in the part to be preserved and in that to be excised and transplanted. Furthermore, semi-isolated perfusion of the left side after separation of hilar structures and dissection of the left hepatic vein during dissection of the parenchyma would also be feasible; a certain amount of the HTK–Bretschneider solution, with its low potassium content, can be tolerated even if it enters the systemic circulation. These remarks should not be misinterpreted as an argument in favour of partial liver donation from a living relative. However, the feasibility and low risk of such a step is indicated by several experiments[25] and by splitting liver graft procedures (Reference 26; H. Bismuth, personal communication; C. Broelsch, personal communication) complemented by the techniques described here It is known that, particularly in Japan where cadaveric liver grafting is still difficult to introduce, great interest is being devoted to the technical considerations of partial liver transplantation from a living relative.

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ADDENDUM

Since submitting this article we have performed further two *ex situ* resections and three *in situ* resections of hypothermically perfused and vascularly isolated livers. Both patients resected *ex situ* had a hepatocellular carcinoma, one of them a recurrence after hemihepatectomy. The three patients resected *in situ* after hypothermic perfusion and vascular isolation suffered from hepatocellular carcinoma, metastases from colonic carcinoma and metastases from a hypernephroma, respectively. The postoperative courses of all five patients were uneventful.

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Hepatic resection for colorectal secondaries

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A postal survey of consultant surgeons in England and Wales was carried out to assess current attitudes towards screening for and treatment of hepatic metastases from primary colorectal carcinoma. The results showed that pre-, intra- and postoperative screening were inadequate. There was no consensus as to which patients would benefit from major hepatic resection for colorectal liver secondaries. Fewer than one-third of potentially operable patients underwent liver surgery.

Keywords: Colorectal carcinoma, hepatic metastasis, hepatic resection

Colorectal cancer is a common disease which afflicts 20 000–30 000 patients in England and Wales every year[1,2] Despite the relatively good prognosis often associated with colorectal cancer, distant spread, particularly to the liver, remains a major problem. In this country up to one-quarter of those under going laparotomy for colorectal cancer have synchronous hepatic metastases[3]. Moreover, at the time of death, hepatic involvement is present in 40–70 per cent of patients[4,5]. Median survival in untreated patients is between 4 and 18 months[6–9], and few (<10 per cent) survive 3 years or more. There are sporadic reports of patients with solitary liver secondaries surviving 5 years[10], although most of these lesions are not biopsy proven[10].

Despite the use of chemotherapeutic agents by both systemic and regional means, the overall prognosis for patients with proven hepatic metastases remains poor. Fluoropyrimidines, such as 5-fluorouracil (5-FU) and doxifluridine, are useful in the treatment of patients with colorectal metastases[11]. Both drugs have a higher response rate when given by continuous hepatic artery perfusion but liver toxicity is the limiting factor. There is no evidence that survival rates are significantly prolonged in patients receiving intra-arterial chemotherapy, although a slight improvement in median survival to 18 months has been seen[11]. There is little convincing evidence of benefit from either single agent or combination systemic chemotherapy[12].

Hepatic artery ligation does not significantly prolong survival[13–15] when compared with untreated patients, although in symptomatic patients it may have a role in the relief of pain due to large tumour masses[16]. Hepatic artery ligation and cytotoxic infusion may give symptomatic relief and a slight improvement in median survival[12,17,18] The combination of hepatic artery ligation and portal vein cytotoxic perfusion with 5-FU[19,20] has been reported to be more effective than either method alone though the median survival was only 10 months in all patients in one series[20].

Irradiation may be used to palliate patients in pain, but there is no evidence that overall survival is improved at a dose safe for the liver[20].

There is increasing evidence that selected patients with metastatic disease amenable to surgical resection may be offered worthwhile palliation and possible cure. A recent multicentre survey[10] demonstrated a 33 per cent 5-year survival rate in 859 patients following resection of hepatic metastases from primary colorectal cancer. Similarly, Adson[21] achieved a 25 per cent overall 5-year survival rate in 141 patients undergoing resection of hepatic secondaries, in the subgroup without extrahepatic disease survival was 46 per cent at 5 years. The opportunity for long-term survival is matched by the fact that major hepatic resection may be performed safely with low morbidity and mortality[10,21–27]

The natural history of untreated cancer is the standard against which the effectiveness of any treatment should be measured, but this is seldom possible today when little is left to nature. The value of resection demonstrated in large series in the USA has left surgeons unwilling to use untreated controls in prospective studies and natural history has, inevitably, been studied retrospectively. Adson[21] has shown that the survival curves of patients with biopsy proven solitary and multiple (<4) unilobar metastases are significantly improved by resection.

We must therefore address ourselves to the following questions. Are we following our patients carefully so that we might detect early resectable hepatic metastases? Once detected, are we offering suitable patients hepatic resection? We were interested in current surgical practice and therefore undertook a postal survey of all consultant surgeons in England and Wales.

Method

In 1987 a questionnaire and covering letter were sent to all consultant surgeons in England and Wales. The questions were

1 Do you treat patients with colorectal cancer? YES/NO
 (a) Preoperative*
 (b) Peroperative*
 (c) Postoperative*.
 * Please indicate methods used
3. Would you consider surgical excision of liver secondaries from colorectal cancer?
 (a) Never
 (b) Only if solitary
 (c) If technically feasible
4 How many cases of surgical excision of liver secondaries from colorectal cancer have you performed in the last year?
 (a) Myself
 (b) Referred elsewhere.
5 If surgery was not feasible would you consider other options?
 (a) Intravenous chemotherapy
 (b) Regional chemotherapy
 (c) Hepatic artery ligation or embolization
 (d) Other means.

Results

Treatment of colorectal cancer

Of the 952 questionnaires sent, 651 were completed while 301 surgeons did not reply, a response rate of 68 per cent. The results of this survey are based on the replies of the 632 consultant surgeons who treated patients with colorectal cancer.

Screening

Preoperative screening was carried out by 443 surgeons (70 per cent). Of this group ultrasound screening was used by 307 surgeons while 68 used liver function tests alone. Thirteen surgeons used other methods such as isotope scanning ($n=7$), computed tomographic (CT) scanning ($n=2$) and measurement of the hepatic perfusion index ($n=2$); 56 did not specify the method used.

Operative screening was carried out by 460 surgeons (73 per cent) This was done by palpation though 65 surgeons

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combined with this careful inspection. Only ten surgeons used intraoperative ultrasound while 27 practised operative biopsy of suspicious liver lesions.

Postoperative screening was used by 181 surgeons (29 per cent), while a further 119 (19 per cent) said they would investigate if clinically suspicious. Of the 181 surgeons who screened after operation, 105 (17 per cent) used ultrasound, 30 (5 per cent) used serial liver function tests, 29 (5 per cent) used serial carcinoembryonic antigen (CEA) levels and five used either isotope scanning or CT scanning; 12 did not specify the method used.

Surgical excision/criteria for surgery

Ninety-three surgeons (15 per cent) said that they would never consider surgery for hepatic metastases. A further 393 (62 per cent) said that they would consider surgery only if the secondary deposit was solitary. Fewer than one-quarter of surgeons indicated that technical feasibility was the criterion used for patient selection for hepatic resection.

Number of hepatic resections performed/year and number of surgeons performing these

One hundred and sixty-eight surgeons (27 per cent) had performed 354 liver resections for colorectal secondaries in the preceding 12 months. The number of resections performed ranged from one to 20 (*Figure 1*), with a mean of two resections per surgeon Sixty-two surgeons referred their patients elsewhere for major hepatic resection.

Other treatment

If surgery was not deemed feasible, 424 surgeons (67 per cent) said they would consider one or more other options: 260 (41 per cent) would use intravenous chemotherapy, 134 (21 per cent) would use regional chemotherapy, 169 (27 per cent) favoured hepatic artery ligation or embolization and 95 (15 per cent) opted for one of the following: radiotherapy ($n = 13$), oral 5-FU ($n = 11$), cryosurgery ($n = 1$), intraperitoneal chemotherapy ($n = 2$), intermittent hepatic artery compression ($n = 1$), hepatic perfusion with urea ($n = 1$), laser treatment ($n = 1$) or referral to a medical oncologist ($n = 25$)

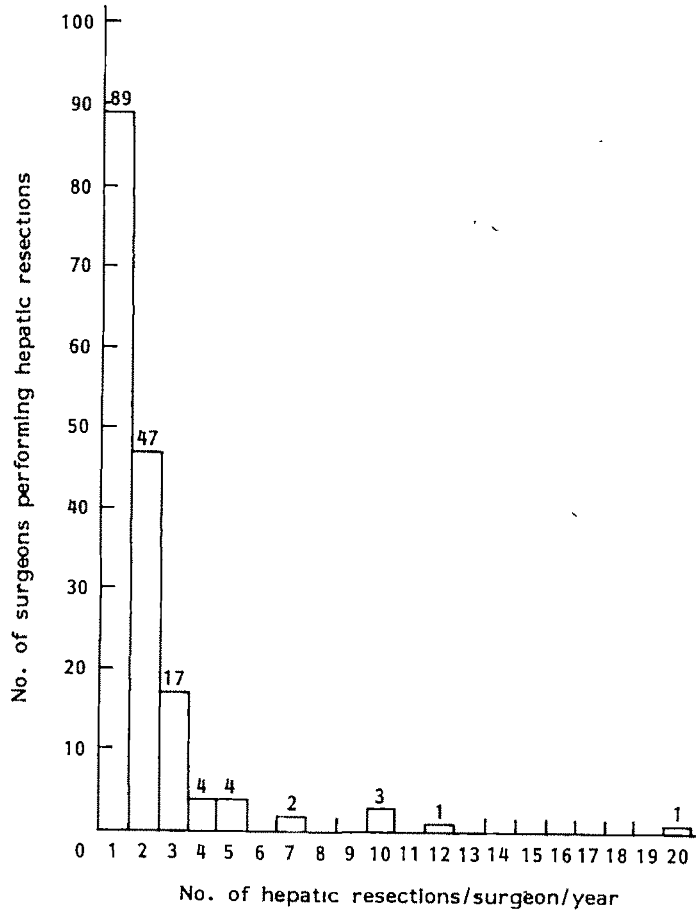

Figure 1 *Histogram showing distribution of hepatic resections in England and Wales per surgeon per year*

Discussion

The justification for surgical resection of colorectal liver secondaries has recently been reviewed in detail in this journal[28], and in several large American series[10,21,23–27]. Adson[21] in a retrospective study estimated that 27 per cent of patients with biopsy proven hepatic metastases were suitable for hepatic resection, and Sugarbaker[27] similarly found that 25 per cent of patients with liver metastases were resectable. Of approximately 20 000 new cases of colorectal cancer each year in England and Wales about 50 per cent will develop hepatic metastases, and of these 10 000 patients at least 10 per cent will have resectable liver lesions. Therefore, in England and Wales alone, 1000 patients each year may be suitable for resection of hepatic secondaries. With reference to the above, this may be a conservative estimate. Our survey suggests that only one-third of suitable patients are being offered hepatic resection. Inadequate screening and failure to consider surgery are important factors contributing to this disparity

Although more than two-thirds of surgeons screened before operation, only half did so effectively using ultrasound, isotope scanning or CT scanning[29–31]. Methods such as liver function tests are less reliable[31]. Despite the ease of palpation only two-thirds of surgeons examined the liver at the time of surgery. Moreover, only ten used intraoperative ultrasound, a method that has many advantages[32,33].

During postoperative follow-up 19 per cent of surgeons were prepared to investigate patients only when they developed symptoms. However, by the time patients are symptomatic, hepatic secondaries are often large, making resection formidable. Radical clearance at the resection margin is more difficult to achieve Seventeen per cent of surgeons screen their patients after operation by regular liver ultrasound and a further 5 per cent rely on serial CEA estimations. Serum CEA, though not uniformly sensitive or specific, is a reliable marker of recurrent colorectal cancer[34,35]. However, serum CEA is related to tumour bulk and it may be the case that CEA-indicated recurrence is beyond cure desite the earlier warning[36,37]

What should we be doing with regard to screening for liver metastases in colorectal cancer? There are no guidelines. Of the options, ultrasound has the advantage of accuracy and availability. This may be combined with serial CEA estimations.

Failure to consider surgery may stem from the belief that major hepatic resection is dangerous and confers no survival advantage. There is evidence that hepatic resection of colorectal secondaries is worthwhile with many large series demonstrating 5-year survival rates of 20–45 per cent[10,21,23,26,27]. A consensus is emerging as to who is likely to benefit[10]. Patients with two or three deposits resected do nearly as well as patients with a solitary secondary removed. Early data from some centres indicate that the three deposits may involve both lobes as long as radical resection is accomplished[10,21]. An absolute contraindication to hepatic resection is the presence of inoperable extrahepatic malignancy[10,21]. The results of this survey imply that a majority of surgeons in England and Wales might need to reconsider their selection criteria for hepatic resection of colorectal secondaries

In our survey we did not ask for details of morbidity and mortality following hepatic resection. Two factors must be considered. First, it is necessary to perform surgery with results compatible with the best centres in the world. Mortality rates should be comparable with those after colonic resection and should certainly be less than 5 per cent[10,21–27]. Secondly, it is essential to resect with a clear 1 cm margin of normal liver tissue so as to confer survival benefit[10,21]. Of the 27 per cent of surgeons performing hepatic resection the mean number of resections per surgeon per year was two, with only a few surgeons performing ten resections a year (*Figure 1*). If we are to improve results in this field, expertise should be concentrated in specialist centres, fully equipped with essential items such as the CUSA (Cavitron Ultrasonic Surgical Aspirator, Valley Lab., UK)[38] and intraoperative ultrasonography[32,33].

The results of this survey on hepatic resection of colorectal metastases suggest that surgeons in England and Wales are not screening patients as well as they might, and that more patients could be considered for hepatic resection.

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Endoscopic sphincterotomy in hepatic hydatid disease open to the biliary tree

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Communication with the biliary tree is the most common complication of hydatid disease of the liver and up to a few years ago surgery was the only way to treat it successfully. The introduction of endoscopic sphincterotomy represented a great advance in the management of this disease. We report the results obtained with this technique in ten patients after surgical treatment of hepatic hydatid disease open to the biliary tree. The results were satisfactory in all cases, with no morbidity or mortality. Endoscopic sphincterotomy is now the first choice treatment for surgical complications of hepatic hydatid disease open to the biliary tree, as well as the drainage procedure of choice in patients with cholangitis due to hydatid disease.

Keywords: Hepatic hydatid cysts, intrabiliary rupture, endoscopic sphincterotomy

Hydatid disease is a parasitic infection caused by *Echinococcus granulosus*. Man is an intermediate host who acquires the disease by ingesting the parasite eggs. Cysts, which are larval forms of the parasite, subsequently develop. The liver is the viscus most commonly affected by *Echinococcus* (50–70 per cent of cases)[1–3], and rupture of the cysts is the most frequent complication. In 5–25 per cent of cases, communication with the biliary tree is established[4–6].

Endoscopic retrograde cholangiopancreatography represents a great advance in the diagnosis of this complication, a diagnosis previously based on laparotomy[7]. More recently, endoscopic sphincterotomy has proved a valid alternative in the treatment of hepatic hydatid disease open to the biliary tree, both in the preoperative and postoperative situation Before surgery the general condition of the patient may be improved, allowing a better chance of a successful surgical outcome After surgery it may allow the definitive treatment of surgical complications and obviate the need for a second operation.

Patients and methods

From January 1981 to July 1988, a total of 2622 endoscopic retrograde cholangiopancreatographies and 344 endoscopic sphincterotomies were carried out at the Gastroenterology Unit of our hospital Ten of these sphincterotomies had been performed because of hepatic hydatid disease open to the biliary tree (*Figure 1*) which had been surgically treated *Table 1* shows the postoperative symptoms that justified endoscopic sphincterotomy as well as the findings at the endoscopic retrograde cholangiopancreatography carried out previously

There were eight female patients and two male patients, with a mean age of 50 years (range 17 to 70) The interval between the onset of symptoms and surgery varied from a few days to several years. Indications for endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy were as follows persistent drainage of bile through the catheter placed in the residual cyst cavity (seven cases), a clinical and biochemical picture of cholangitis (two cases), and relapsing pancreatitis after surgery (one case) Endoscopic retrograde cholangiopancreatography showed an external biliary fistula in all seven cases in which bile had been flowing through the drainage catheter (cases 1, 2, 4, 5, 6, 8 and 9), in one of these cases cholangiography also showed stenosis at the sphincter of Oddi (case 6). Stenosis at the papilla was also seen in one patient with acute cholangitis (case 10) and in the patient with relapsing pancreatitis (case 7) In case 3 (acute cholangitis) several luminal defects presumed to be hydatid fragments were shown within the main bile duct.

To date the patients have been followed for a mean of 32 months (range 6–84 months) to assess the response to endoscopic treatment and to detect late complications

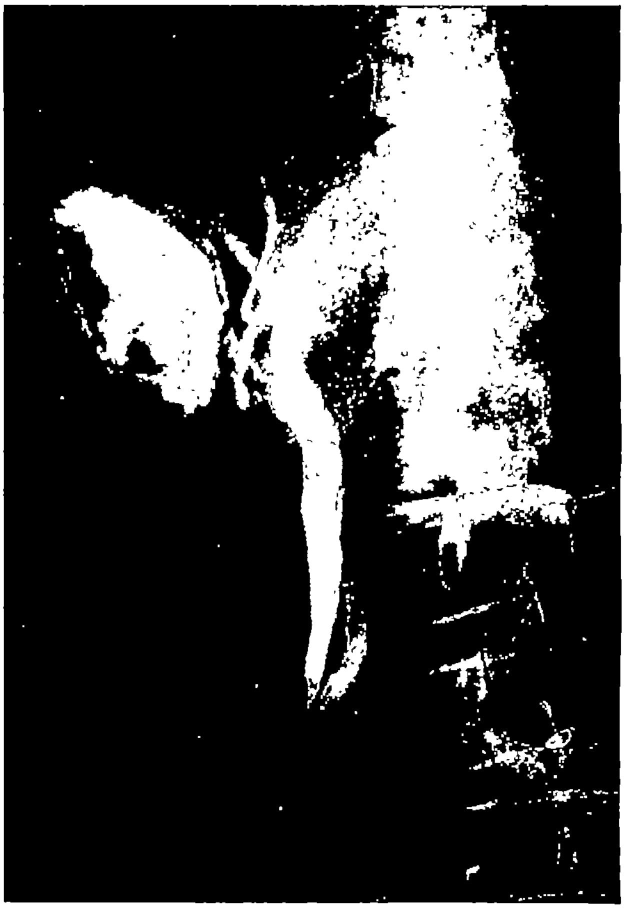

Figure 1 *Endoscopic retrograde cholangiopancreatograph of case 4 showing a communication between the biliary tree and an irregular cavity from which contrast is flowing through a fistulous tract to the abdominal wall*

Results

The results obtained by endoscopic sphincterotomy in these patients were as follows (*Table 2*).

1. Spontaneous closure of the fistulous tract in all seven cases with an external fistula, the average time to closure being 1 month (18–43 days)

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Table 1 *Clinical features, indications and findings at endoscopic retrograde cholangiopancreatography in patients with biliary complication of hydatid disease*

Case	Age	Sex	Symptoms	Endoscopic retrograde cholangiopancreatography
1	17	F	EBF	Fistulous tract
2	25	F	EBF	Fistulous tract
3	48	M	Cholangitis	Vesicles in CBD
4	48	F	EBF	Fistulous tract
5	52	F	EBF	Fistulous tract
6	55	F	EBF	Fistulous tract and papillary stenosis
7	60	M	RP	Papillary stenosis
8	60	F	EBF	Fistulous tract
9	62	F	EBF	Fistulous tract
10	70	F	Cholangitis	Papillary stenosis

EBF, external biliary fistula, CBD, common bile duct, RP, recurrent pancreatitis

Table 2 *Results of endoscopic sphincterotomy*

Case	Endoscopic retrograde cholangiopancreatography	Results after endoscopic sphincterotomy
1	Fistulous tract	Closed
2	Fistulous tract	Closed
3	Vesicles in common bile duct	Vesicles eliminated, cholangitis resolved
4	Fistulous tract	Closed
5	Fistulous tract	Closed
6	Fistulous tract and papillary stenosis	Closed
7	Papillary stenosis	No recurrence of pancreatitis
8	Fistulous tract	Closed
9	Fistulous tract	Closed
10	Papillary stenosis	Cholangitis resolved

2. The biliary tract was decompressed in cases with papillary stenosis with closure of the external biliary fistula (one case) and relief of acute cholangitis (one case) Stenosis of the papilla in the patient with recurrent pancreatitis following surgery for hydatid disease was considered to be the cause of relapsing pancreatic inflammation in the absence of other causes; this patient remained free from symptoms in the subsequent 5 years of follow-up

3. Disappearance of biliary obstruction and acute cholangitis in the patient with intraductal hydatid fragments.

Endoscopic sphincterotomy was achieved without complications. None of the patients required a second sphincterotomy

Discussion

Before the introduction of endoscopic sphincterotomy[8,9], the abnormalities of the distal bile duct could only be managed by surgical techniques which carried a 1·4–4·7 per cent mortality rate[10]. Initially endoscopic sphincterotomy was carried out for therapeutic purposes in patients with residual choledocholithiasis or inflammatory stenosis of the sphincter of Oddi The excellent results achieved in these two conditions prompted a progressive widening of the indications of this technique.

Rupture into the biliary tract is a common complication of hydatid disease of the liver, the incidence of which ranges between 5 and 25 per cent in different series[4–6] On the other hand, external biliary fistula not infrequently develops following surgical drainage of cysts. This is probably because it is easier for bile to flow into the residual cavity than through the papilla of Vater[11]. Barros reported a 3·8 per cent incidence of external biliary fistula in a series of 212 patients operated on because of hydatid disease of the liver[3].

The indications for endoscopic sphincterotomy in patients with biliary complications of hydatid disease of the liver can be subdivided as follows.

1. Preoperative – the presence of daughter vesicles or hydatid debris in the common bile duct or acute cholangitis even if endoscopic retrograde cholangiopancreatography does not show communication between the cyst and the biliary tree
2. Postoperative – inflammatory stenosis of the sphincter of Oddi, external biliary fistula, intrabiliary hydatid remnants, and secondary sclerosing cholangitis.

There are few reports in the literature of the use of endoscopic sphincterotomy in the treatment of intrabiliary rupture of hydatid disease of the liver, although the series are small the results seem promising[11–13]. In our experience of this technique in ten patients closure of an external biliary fistula (*Figure 1*) was generally achieved within a month of sphincterotomy In the remaining three cases sphincterotomy was also successful as cholangitis subsided in two of them and pancreatitis did not recur in the third. There has been no morbidity or mortality in this series.

In Ponchon *et al.*'s series of nine patients with intrabiliary rupture of hydatid cysts of the liver, endoscopic sphincterotomy was successful in all cases and there were no complications or mortality[12]. In three patients sphincterotomy was performed before operation because of acute cholangitis in relation to hydatid elements within the common bile duct. In the remaining six cases sphincterotomy was carried out after surgery (three patients with cholangitis and intrabiliary hydatid debris, two patients with external biliary fistula and one case of secondary sclerosing cholangitis). Al Karawai *et al.* reported on the successful and uncomplicated treatment by endoscopic sphincterotomy in one patient with obstruction of the main biliary tract by spontaneous rupture of hydatid cysts[13]. Recently, Del Olmo *et al.* have reported seven cases of external biliary fistula, four of which were due to hydatid disease; all were successfully managed by endoscopic sphincterotomy[11]

We conclude that endoscopic sphincterotomy is a safe and effective technique in the management of biliary complications of hepatic hydatid disease.

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Methyl-tert-butyl-ether for treating bile duct stones: the British experience

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Methyl-tert-butyl-ether (MTBE), infused via a nasobiliary catheter, was used to treat 33 patients with bile duct stones in nine units around Britain. MTBE contributed to success in 12 (36 per cent) cases: seven passed stones spontaneously during MTBE infusion and five had partial stone dissolution allowing subsequent endoscopic extraction. MTBE was non-contributory in 21 (64 per cent) cases: four passed stones after MTBE was stopped, six were treated by subsequent endoscopic techniques without evidence of dissolution, seven underwent surgery, and four were treated conservatively (with one death). In at least ten of the 21 cases in which MTBE was non-contributory, pigment stones were present. Forty-two complications occurred in 26 (79 per cent) patients. The efficacy of MTBE for treating bile duct stones might be improved by better methods of instillation and, since success may be related to technique, the use of MTBE should be restricted to units familiar with this chemical.

Keywords: Choledocholithiasis, ERCP, methyl-tert-butyl-ether

Methyl-tert-butyl-ether (MTBE) is an aliphatic ether capable of rapid dissolution of cholesterol gallstones both *in vitro*[1] and *in vivo*[1,2]. It has been successfully applied to the treatment of gallbladder stones by means of a percutaneous transhepatic cholecystostomy catheter, introduced under local anaesthesia[3–5]. Its high success rate in this context is particularly attributable to: a high incidence of cholesterol stones in the gallbladder[6]; the ability to exclude by radiographic means most patients with calcified stones and/or pigment stones which are resistant to MTBE dissolution[1,7–9]; and the ability to effect an almost complete exchange of bile with MTBE and undertake rapid stirring of the solvent within the relatively confined gallbladder compartment[1,6,10].

The treatment of bile duct stones may not be so straightforward because of the variable prevalence of cholesterol stones in this situation[11–13], and potential difficulties in effecting optimum contact between MTBE and the gallstones[14]. Relatively few cases have been reported, and with conflicting results[2,7,14–21]. Because of this, it was decided to undertake a survey of the use and efficacy of MTBE for dissolving bile duct stones in British centres.

Patients and methods

A detailed postal questionnaire was sent to 190 gastroenterologists working in 79 major hospitals in the UK. To the best of our knowledge all doctors using MTBE for stone dissolution were included. The questionnaires were despatched in April 1988 and information was finally collated in December 1988. MTBE therapy was defined as successful if there was objective evidence that it had contributed to complete clearance of stones from the bile ducts without resort to surgery. This included partial dissolution or complete stone disappearance while MTBE was being given, as determined by cholangiography. 'Softening' of stones in the absence of a reduction in size was not considered to be sufficiently objective.

Statistical analysis was performed using the two-tailed Mann–Whitney U test for continuous variables and the χ^2 test with Yates' correction for categorical variables. Significance was taken as $P<0.05$.

Results

Replies

Eighty-one (43 per cent) replies were received. Ten units had used MTBE for bile duct stone dissolution and nine provided the information as requested. The other unit had published results in abstract form[17], but they have not been included in this analysis.

Patients

Treatment was attempted in 33 patients (Glasgow, $n=14$; Birmingham (two units), $n=7$; Leicester, $n=4$; Manchester, $n=2$, Plymouth, $n=2$; Oxford, $n=2$; Reading, $n=1$; and Leeds, $n=1$). The median age was 77·5 years (range 53–95 years), and 24 patients were women. In 21 (64 per cent) patients the gallbladder was still present, 11 patients had undergone a remote cholecystectomy and one presented in the immediate postcholecystectomy period.

Twenty-eight (85 per cent) patients were considered to be at high risk for surgery. The following 40 medical risk factors were present in them. cardiovascular, $n=19$; respiratory, $n=10$; gross obesity, $n=3$, acute cholangitis, $n=3$; diabetes mellitus, $n=1$, cirrhosis, $n=1$; renal failure, $n=1$; dystrophia myotonica, $n=1$; and hypothyroidism, $n=1$.

Treatment

A nasobiliary catheter was inserted following endoscopic retrograde cholangiopancreatography (ERCP) in all cases. An endoscopic sphincterotomy was performed in 31 cases, although this was judged to be inadequate in five cases (because of previous Pólya gastrectomy in one case, profuse bleeding in another, and for other technical reasons in three others).

Two patients received treatment with mono-octanoin (Moctanin®, Ethitek Pharmaceuticals Company, Illinois, USA) to dissolve the stones[22] before MTBE therapy. Eight centres used a manual technique of aspirating bile followed by instillation of MTBE, whereas one centre used a cyclical pump device by which this was undertaken automatically. The manual technique was used in 29 cases, with 1–15 treatment periods; the total duration of treatment was 1·5–42 h and the total volume infused was 30–480 ml. The mechanical device was used in four cases with 6–20 treatment periods, the total duration of treatment being 18–40 h, and the total volume cycled was 27–72 litres.

Outcome

MTBE was considered to have contributed to successful treatment in 12 (36 per cent) cases. In seven, spontaneous clearance was achieved while MTBE was being infused. In five

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cases there was clear radiological evidence of partial stone dissolution varying from 22 percent to 66 percent of the maximum cross-sectional diameters of the stones. This facilitated clearance at repeat endoscopical therapy, stone 'softening' was also considered to have occurred in four of these cases.

MTBE was considered not to have contributed to treatment in 21 (64 per cent) cases. In none of these cases was stone dissolution apparent on repeated cholangiography and MTBE infusion was stopped. Four patients subsequently passed stones spontaneously. In six cases stones were successfully extracted following further endoscopic treatment. In two of these cases partial stone dissolution was achieved with modified mono-octanoin (GMOC) and bile acid–ethylenediamine tetra-acetic acid (BA-EDTA) infusion[23], followed by crushing with a mechanical lithotriptor. In the other four of these six cases, stones were successfully removed by further endoscopic treatment; in only one of these cases were the stones believed to have been 'softer' after MTBE use.

Seven patients underwent surgical choledocholithotomy with uneventful recovery. Three patients were at such high risk that no surgical treatment was undertaken without adverse effects. Another patient who failed MTBE therapy died from cholangitis while awaiting surgery.

Of the two patients who did not have an endoscopic sphincterotomy at the outset, one went on to have surgery and the other had successful repeat endoscopic treatment. Of the five patients with inadequate endoscopic sphincterotomies, two had surgery, one had an adequate sphincterotomy and mechanical extraction, one passed the stones spontaneously and one was treated conservatively. In none of these seven cases was there any evidence of stone dissolution or 'softening'.

Table 1 *Details of MTBE treatment in those cases in which MTBE was considered to have contributed to a successful outcome and in those in whom it was considered not to have contributed to a successful outcome*

	MTBE contributory ($n=12$)	MTBE non-contributory ($n=21$)
Remote cholecystectomy	6	5
Bile duct diameter (mm)	20 (10–26)	15 (5–28)
Maximum stone diameter (mm)	18 (10–26)	15 (8–45)
Hand instillation	12	17
Mechanical installation	–	4
Treatment periods	4 (2–5)*	5 (1–20)
Duration (h)	8 (4–10)	8 (1·5–40)
Volume (ml)	50 (30–80)*	145 (30–72 000)

Values are median (range); MTBE, methyl-tert-butyl-ether, * differences were significant ($P<0{\cdot}05$), all other differences not significant, Mann–Whitney *U* test

Patients in whom MTBE therapy was considered to have been non-contributory had significantly more MTBE administered than those in whom it was useful (*Table 1*) Eleven of the 12 successful cases came from one centre (Glasgow), a significant difference in success rate when compared with all other units ($\chi^2=15{\cdot}9$, degrees of freedom (d.f.) = 1, $P<0{\cdot}001$).

Stones were recovered in 10 of 21 (48 per cent) treatment failures and all were pigment stones as judged by inspection[6]. This was confirmed by biochemical analysis in three, infrared spectroscopy in one and failure to dissolve the stones with MTBE *in vitro* in another case. Thus MTBE contributed to successful treatment in 52 per cent of cases in which definite pigment stones were excluded.

Forty-two complications occurred in 26 (79 per cent) patients: drowsiness, $n=13$; transient elevation of liver enzymes, $n=8$; pain on commencement of MTBE, $n=5$; nausea, $n=6$; anorexia, $n=5$; hypotension, $n=2$; headaches, $n=1$; palpitations, $n=1$; and angina, $n=1$. With the exception of the angina, the complications were not serious enough to stop MTBE treatment Drowsiness and anorexia were constant features of the four cases having mechanical instillation which necessitated the use of intravenous infusions in order to maintain hydration.

Discussion

The distinction between the clinically beneficial contribution of MTBE from the delayed but purely mechanical effects of endoscopic sphincterotomy and nasobiliary catheter insertion inevitably involves some subjective assessment. In stating that MTBE contributed to success in 12 (36 per cent) cases, we have assumed that stone dissolution and/or 'softening' occurred in the seven cases in which stones completely disappeared during MTBE therapy Dooley *et al.*[17] have described stone 'softening' without reduction in stone volume in two cases, although mechanical extraction was necessary in order to clear the ducts. Brandon *et al*[18] also described two similar cases but they did not state whether mechanical extraction had been attempted before MTBE infusion.

It is well recognized that stones which have not been extracted from the bile duct at the first endoscopic attempt may pass spontaneously or be extracted readily at succeeding attempts[24,25]. For this reason we have regarded as failures of MTBE treatment the four cases in which stones were passed

Table 2 *Collected results of the use of MTBE in the treatment of bile duct stones. Success is as stated by the authors of each series*

		Route of MTBE administration					
Series	*n*	NBC	PTHC	T T tract	Dissolution or disappearance	Mechanical intervention	Success
Allen *et al*[1]	1	1	–	–	1	0	1
Leuschner *et al*[7]	1	1	–	–	0	0	0 (1*)
Bonardi *et al*[15]	6	3	3	–	5	1	6
Di Padova *et al*[14]	3	–	–	3	0	1	0 (3†)
Brambs *et al.*[16]	1	–	1	–	1	0	1
Dooley *et al*[17]	4	4	–	–	0	3	2 (2*)
Brandon *et al.*[18]	10	–	10	–	8	7	9 (3*)
Bories *et al*[19]	12	12	–	–	7	6	7
Carrick *et al*[20]	3	–	–	3	3	2	3
Present	33	33	–	–	12	13	12(1*,2†,4§)
Total	74	54 (73%)	14 (19%)	6 (8%)	37 (50%)	33 (45%)	41 (55%)

MTBE, methyl-tert-butyl-ether; NBC, nasobiliary catheter, PTHC, percutaneous transhepatic cholangio-catheter; T T tract, T tube tract catheter; * death following MTBE failure, † dissolution with mono-octanoin; § success due to stone 'softening' spontaneously after MTBE was stopped and the six cases having endoscopical clearance at a subsequent attempt without evidence of a reduction in stone size

The current series represents 45 per cent of the published international experience with MTBE for bile duct stones (*Table 2*). In some cases the definitions of success may have been more liberal than in the present series. Accepting these, the overall success rate is 41 of 74 (55 per cent) cases and 33 of 41 (80 per cent) patients required additional mechanical intervention.

At least ten of the MTBE treatment failures in this series had pigment stones. Thus, at least 30 per cent of the whole series of 33 patients had stones which were resistant to MTBE dissolution[1,7], giving a 'true' MTBE success rate of at least 52 per cent. The incidence of pigment stones in the bile duct in Western patients varies from 24 to 70 per cent, the higher values tending to be found in remote cholecystectomy patients[11–13]. This alone must limit the overall usefulness of MTBE. Treatment with agents which may affect brown pigment stones should be tried[6,22], and alternating GMOC and BA-EDTA solutions[23] were used with some success in two patients.

Because of the low viscosity and low density of MTBE[14], contact between the stones and MTBE may be poor Thus, substituting mono-octanoin which has a higher density than bile[26] resulted in successful dissolution in three cases in which MTBE failed[14]. Part of the difficulty in judging the true benefit of MTBE in the ten cases reported by Brandon *et al.*[18] was that mono-octanoin was also used intermittently in four of their patients.

Improved contact between MTBE and the bile duct stones by constant stirring is required to achieve maximum benefit[10]. Although this might be achieved by a mechanical pumping device[27], this has yet to be proven; a similar (albeit inferior) mechanical technique was unsuccessful in all four cases in this series. The use of a balloon to prevent egress of MTBE from the lower bile duct may be important[18] Even in the absence of such techniques, attention to detail, particularly the aspiration of bile before each instillation and the positioning of the patient, may account for the high success rate of the Glasgow unit Increased levels of cholesterol in MTBE during successful dissolution may be quickly detected by thin layer chromatography or the appearance of cholesterol crystals after a few drops of MTBE are placed on a glass slide and allowed to evaporate. When stones with a very high cholesterol content are dissolving, cholesterol crystals can be seen to form just above the effluent bile/MTBE interface if the solution is left standing in a glass tube. Thus, it is possible to detect MTBE dissolution activity during or just after the first treatment session Cholangiography can also give supportive evidence of stone dissolution.

The common side-effects of MTBE are due to spill-over into the intrahepatic canaliculi and duodenum resulting in systemic absorption. These side-effects, of which drowsiness is the commonest, are usually reversible within 2–3 h of stopping the MTBE Prolonged and excessive absorption will result in anorexia, which is partly central in origin and partly due to irritation of the oropharyngeal membranes. It is essential that such patients receive intravenous fluids as well as being rested overnight from the treatment. Severe haemolysis with coma and acute renal failure has been reported in one patient with 'spill-over' of only 15 ml MTBE[28]. In the present series, 100 ml or more have been lost into the duodenum without such side-effects. Acute cholangitis may result from a rise in the intrabiliary duct pressure due to excessive infusion in a closed system The death reported previously (Reference 7 and U Leuschner, personal communication), as well as the death in this series, however, were both due to failure to eliminate stones from the biliary tree rather than due to the MTBE *per se*.

The surgical mortality rate from bile duct stones in patients with concomitant medical problems remains high[29,30]. These patients need to be selected for non-operative forms of treatment. Both the advanced age and associated medical problems of the patients in this series would indicate conformity with this approach. There will inevitably be a need for methods to supplement interventional radiological or endoscopic methods of mechanical extraction. Although more successful, mechanical aids, such as extracorporeal shock wave lithotripsy[31] and endoscopic laser lithotripsy[32], are expensive and not generally available Endoscopic electrohydraulic lithotripsy[33] and ultrasound lithotripsy[34] have proved to be disappointing. Because of their ease of application and relatively low cost, chemical agents for dissolving bile duct stones are still required Difficulties remain with the use of MTBE for treating bile duct stones; unless they are overcome its use should be restricted to specialist centres with experience in the use of this chemical.

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Announcement

Joint College Commission on Acute Pain

The College of Anaesthetists and Royal College of Surgeons have established a Commission to examine in depth the management of pain after surgery. The objectives of this Commission will be as follows:

1 To review currently available methods for the relief of postoperative pain. Advantages and disadvantages of each method and the resources required for implementation will be considered. The following techniques will be examined:
   (a) opiods, including routes of administration and patient controlled analgesia;
   (b) non-steroidal analgesics;
   (c) local anaesthesia;
   (d) transcutaneous stimulation;
   (e) inhalation analgesia,
   (f) acupuncture,
   (g) counselling;
   (h) surgical techniques which may reduce postoperative pain.
2. To reach a consensus on the suitability of these methods.
3 To produce guidelines on safe practice.
4. To identify the best directions for development and priorities for funding.
5 To convey findings by the production of a report.

The Commission is seeking the opinions and experience of those surgeons and anaesthetists with an interest in the field Practitioners who wish to communicate with the Commission should write to the secretary: Mr Craig Duncan, Royal College of Surgeons, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK. Alternatively, they should write to the medical secretaries: Dr David Rowbotham, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, UK, or Mr David Crosby, Consultant Surgeon, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, UK.

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Roles of bile and bacteria in biliary peritonitis

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Bile is known to have an adverse effect in peritonitis but the mechanism(s) and site of action of bile are unknown, as are the relative roles of bile and bacteria. The present study was designed to answer some of these questions. Experiments in which rats were injected intraperitoneally and intravenously with bile, Escherichia coli *or saline showed that bile had no systemic toxicity and that it increased the mortality rate only when introduced into the peritoneal cavity together with bacteria. Measurements of peritoneal fluid volumes and blood pressure did not confirm the theory that the increased mortality rate was a consequence of loss of plasma volume into the peritoneal cavity. The number of intraperitoneal bacteria decreased continuously in animals receiving intraperitoneal* E. coli *alone. When bile was added by intraperitoneal injection, the number of intraperitoneal bacteria started to rise at 2 h and then increased steadily with a consequent bacteraemia at 10 h. The number of bacteria per peritoneal phagocyte was significantly lower after intraperitoneal injection of* E. coli *and bile, when compared with injection of* E. coli *alone. It is concluded that bile exerts its detrimental effect within the peritoneal cavity in the presence of bacteria. Bile impairs local host defence in a way that remains unknown and may be related to the detergent–lytic effects of bile salts.*

Keywords: Bile, *Escherichia coli*, peritonitis, peritoneal phagocytes

The consequences of bile peritonitis continue to be severe, especially in acute cholecystitis, with its mortality rate of 8–40 per cent[1–5]. Both clinical and experimental studies indicate that bile in the abdomen has noxious effects and that concomitant bacterial infection may aggravate the peritonitis[5,6]. Culture of intraperitoneal bile following perforated acute cholecystitis demonstrates bacterial growth in three-quarters of the patients, with *Escherichia coli* being the most frequently isolated organism[1,2,5,7].

Three theories have been proposed to explain the adverse effect of bile in the peritoneal cavity: (a) toxic effect of bile salts absorbed into the systemic circulation[8–10], (b) loss of fluid into the peritoneal cavity[11], and (c) impairment of host defence mechanism(s) against bacteria[12,13]. However, the relative importance of these factors remains speculative and the mechanism(s) and sites of action of bile are unknown. For instance, it is uncertain whether bile exerts its adverse effect through local (within the peritoneal cavity) or systemic (after absorption) toxicity. The purpose of this study was to define the roles of bile and bacteria and the site of action of bile in bile peritonitis.

Materials and methods

Male Sprague–Dawley rats (Anticimex, Stockholm, Sweden), weighing 300–330 g, were used in all experiments. Animals were maintained on standard rat pellets (R3, Astra-Ewos, Sodertälje, Sweden) with water *ad libitum* and were housed separately

Experimental design

An intra-abdominal sepsis model, based on the intraperitoneal administration of *E coli*, was used for evaluating the mechanisms and consequences of bile in the abdomen.

The first set of experiments was designed to determine the principal site of the noxious action of bile and the role of bacterial contamination by recording the mortality rate after intraperitoneal and intravenous injections of *E coli* and/or bile in various combinations (seven groups with 15 rats in each) In addition, one group ($n = 15$) received 7 mg cefuroxime (Zinacef®, Glaxo Laboratories Ltd, Greenford, UK) intravenously at 0, 8 and 16 h after induction of peritonitis.

Mean arterial blood pressure was determined in rats receiving intraperitoneal injections of (a) bile and saline, (b) *E coli* and saline, (c) *E. coli* and bile, or (d) saline (control), ($n = 6$ in each group)

The amount of peritoneal fluid was determined at 1 and 10 h after intraperitoneal injection of bile and saline, *E. coli* and saline, or *E coli* and bile ($n = 6$ in each group at each time interval)

Viable counts were determined in the peritoneal fluid and blood at intervals of 0 5, 1, 2, 4 and 10 h after induction of peritonitis by intraperitoneal injection of *E coli* or *E coli* and bile ($n = 6$ at each time interval in both groups)

Peritoneal fluid was sampled for phagocyte counts and determination of the number of ingested bacteria. These determinations were made at intervals of 1, 5, 10, 20 and 30 h after intraperitoneal injection of *E coli* and intervals of 1, 3, 5 and 10 h after intraperitoneal injection of *E coli* and bile ($n = 6$ at each time interval in both groups)

Injection protocol and surgical preparation

Bacterial inocula were prepared to contain 3×10^8 colony forming units (c f.u.) in 1·0 ml Todd–Hewitt broth Pooled sterile bile from the gall-bladder was obtained from patients undergoing elective cholecystectomy and was stored at −70°C until used The bacterial inoculum, bile or sterile saline was injected in a volume of 1 ml each. This volume of bile is proportional to the intraperitoneal accumulation of bile observed in bile peritonitis following acute cholecystitis in humans[5].

All injections and sampling procedures in rats were performed under ether anaesthesia Sterile instruments were used, and the injection or sampling sites were shaved and prepared with povidone-iodine. Intraperitoneal injections were performed through the lower right abdomen using a fine needle. Intravenous injections were performed through a hindlimb vein. Blood was obtained by cardiac puncture Peritoneal fluid was thoroughly sucked out with a Pasteur pipette through a midline laparotomy.

For measurement of blood pressure, a cannula (outer diameter 0 75 mm, Portex Ltd., London, UK) was inserted into a femoral artery at the same time as the intraperitoneal challenge The animals were placed in metabolic cages and blood pressure was determined with Mingograph 7 (Siemens-Elema, Erlangen, FRG) at the start of the experiment (time zero), and at frequent intervals for the following 14 h.

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Bacterial strain and growth conditions

A human isolate of *E coli*, serotype 046 K1 H31, was used. This strain is facultatively anaerobic, lacks haemolysin activity and shows haemagglutination with rat erythrocytes (at 37°C, but not at 20°C) and particle agglutination with collagen type I, fibronectin, vitronectin and laminin (at 37°C). Overnight subcultures in Todd–Hewitt broth were stored in aliquots at −70°C for a maximum of 4 weeks before use. The bacteria were thawed immediately before injection

Quantitative cultures of blood and peritoneal contents were performed aerobically on blood agar. The plates were incubated at 37°C and the colonies were counted after 1–3 days. Before plating, samples were diluted (1·10) with sterile saline; this was repeated five times for blood and nine times for peritoneal samples. Peritoneal contents for bacterial culture were collected by intraperitoneal injection (through a small midline laparotomy) of 10 ml sterile RPMI 1640 medium (Sigma, St. Louis, USA) with heparin (10 international units/ml), followed by gentle agitation for 3 min

Peritoneal phagocytes

Peritoneal washout was performed by injecting 15 ml RPMI 1640 medium with heparin (10 international units/ml) into the peritoneal cavity, through a small midline laparotomy, followed by gentle agitation of the abdomen for 3 min. A sample of 10 ml of the peritoneal contents was sucked out with a Pasteur pipette, centrifuged twice for 10 min at 2000 r.p.m and resuspended in 9 ml RPMI 1640 medium and 1 ml fetal calf serum. The number of phagocytes was estimated by counting in a Burker chamber Viability was 95 (2) per cent (mean (s e.m)) as determined by the Trypan blue exclusion test

The suspension of peritoneal phagocytes was adjusted to give a concentration of 10^6 cells/ml. One millilitre of the suspension was incubated in a well of silicon rubber on an alcohol-washed microscope slide for 60 min at 37°C to allow the phagocytes to adhere to the glass surface[14–17] Two slides were prepared from each animal After incubation, the medium was poured off and non-adherent cells were washed away by quickly dipping the slide five times in Hank's balanced salt solution (Sigma), followed by a 3 s wash in one part protein-buffered saline, two parts distilled water and 1 per cent fetal calf serum. The slides were fixed in methanol, left to dry and then stained with non-specific esterase and Giemsa (Sigma) The number of bacteria per phagocyte was determined using light microscopy by counting the bacteria associated with the phagocyte (intracellular and adherent) in 50 consecutive phagocytes on each slide

Statistical methods

Fisher's exact test was used to compare the rates of survival The Mann–Whitney rank sum test was used for comparison of survival times, blood pressure, peritoneal fluid volumes, bacterial counts and number of bacteria per peritoneal phagocyte Values are mean(s e m) unless otherwise indicated.

Results

Mortality

Mortality rates are summarized in *Table 1*. Intraperitoneal administration of *E coli* alone caused a mortality rate of 27 per cent. The intraperitoneal addition of bile (*E. coli* and bile peritonitis) resulted in a significant increase in mortality rate (87 per cent, $P<0{\cdot}01$ when compared with the intraperitoneal injection of *E coli* alone). This was the only situation in which bile influenced the mortality rate after intraperitoneal or intravenous administration. Intravenous injection of *E. coli* did not result in any deaths, regardless of whether bile was administered or not. Rats did not die following the induction of *E. coli* and bile peritonitis if they were receiving cefuroxime ($P<0{\cdot}001$ when compared with rats not receiving cefuroxime).

Table 1 *Mortality rate in rats following intraperitoneal or intravenous injection of combinations of bile and* E coli

Group ($n=15$)	Route of injection		Mortality	
	Intraperitoneal	Intravenous	Number	Rate (%)
1	*E coli* and saline	Saline	4	27
2	Saline and saline	*E coli*	–	–
3	Bile and saline	Saline	–	–
4	*E coli* and saline	Bile	3	20
5	Bile and saline	*E coli*	–	–
6	Saline and saline	*E coli* and bile	–	–
7	*E coli* and bile	Saline	13	87*
8	*E. coli* and bile	Saline and cefuroxime	–†	–

* $P<0{\cdot}01$ when compared with group 1, † $P<0{\cdot}001$ when compared with group 7

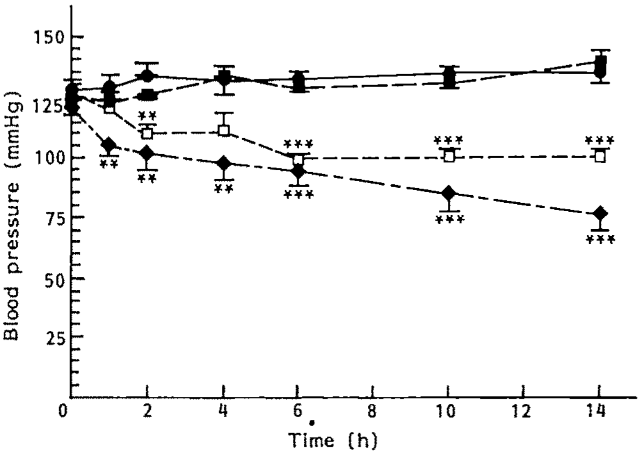

Figure 1 *The effect of bile and* E coli *on mean arterial blood pressure of rats. Values are mean(s.e.m.)* ●—●, *control,* ■--■, *bile;* □--□, E coli, *or* ◆—◆, E. coli *and bile* **, $P<0{\cdot}01$; ***, $P<0.001$ compared with controls

Table 2 *Peritoneal fluid volume in rats following intraperitoneal injection of combinations of bile and* E coli

Intraperitoneal injection ($n=6$)	Peritoneal fluid (ml) at	
	1 h	10 h
Saline and saline	–	–
E coli and saline	0·04 (0·01)	0·01 (0·00)
Bile and saline	0·27 (0·03)†	0·03 (0·01)*
E. coli and bile	0·37 (0·04)†	0·47 (0·09)†‡

* $P<0{\cdot}05$ compared with *E. coli* and saline, † $P<0{\cdot}001$ compared with *E coli* and saline; ‡ $P<0{\cdot}001$ compared with bile and saline

Rats receiving intraperitoneal *E coli* and bile had a more rapid septic course with a shorter survival time (median 12 h, range 9–19 h) than rats receiving intraperitoneal *E. coli* alone (median 17 h, range 16–28 h, $P<0{\cdot}05$).

Clinical signs

Signs of sepsis, including fever, tachypnoea, piloerection, haemorrhagic diathesis and lethargy, were seen in rats challenged with intraperitoneal *E. coli*, 3×10^8 c.f.u., whereas intravenous injection of the same dose of *E. coli* resulted in mild, temporary distress only Administration of bile did not appear to change the clinical picture in rats receiving bacteria. Injection of bile alone did not affect the general condition of the rats.

Blood pressure

The results of blood pressure measurements are given in *Figure 1*. Mean arterial blood pressure was not affected by intraperitoneal bile alone; it decreased moderately and gradually in both *E. coli* and *E. coli* with bile peritonitis ($P<0{\cdot}01$ when compared with controls receiving saline). When compared with *E. coli* peritonitis, blood pressure in *E. coli* and bile peritonitis was significantly lower ($P<0{\cdot}01$) at 1 and 14 h.

Peritoneal fluid accumulation

E coli peritonitis was associated with small amounts of peritoneal fluid (*Table 2*). When compared with *E. coli* peritonitis intraperitoneal bile alone caused a significant increase in peritoneal fluid at 1 h ($P<0{\cdot}001$) but not at 10 h ($P>0{\cdot}05$) after injection. After induction of *E. coli* and bile peritonitis, the volume of peritoneal fluid was similar at 1 h to that seen after intraperitoneal injection of bile alone; subsequently, however, the fluid volume did not decrease but rose to a slightly higher value at 10 h ($P<0{\cdot}001$ for all comparisons). At this time, the volume of peritoneal fluid was more than ten times greater after injection of bile and *E. coli* than after injection of bile alone ($P<0{\cdot}001$).

Viable counts

Figure 2 shows the bacterial counts in the peritoneal fluid and blood of rats with *E. coli* or *E. coli* and bile peritonitis. During the first 1–2 h, the number of bacteria in the peritoneal fluid was similar in both groups. In *E. coli* peritonitis, bacterial numbers continued to decrease. In *E. coli* and bile peritonitis, numbers started to increase after 2 h and were significantly higher than in *E coli* peritonitis at 2, 4 and 10 h ($P<0{\cdot}01$ in all cases).

Bacteraemia was demonstrated only at 0·5 and 1 h after intraperitoneal injection of *E. coli* (*Figure 2*). In *E. coli* and bile peritonitis, *E. coli* was isolated from the blood at all time intervals, except at 4 h after intraperitoneal injection. In addition, in *E. coli* and bile peritonitis, the number of *E. coli* in the blood was higher at 10 h than at earlier times ($P<0{\cdot}01$).

Peritoneal phagocytes

The number of harvested phagocytes increased with time after the induction of peritonitis ($1{\cdot}5\times10^6-6{\cdot}0\times10^6$ cells) and did not differ between *E. coli* and *E. coli* with bile peritonitis. The number of bacteria per peritoneal phagocyte (*Figure 3*) was significantly lower in *E. coli* and bile peritonitis than in *E. coli* peritonitis ($P<0{\cdot}01$ at all time intervals).

Discussion

This study demonstrates that bile is deleterious when given intraperitoneally with *E. coli* but not when it is given alone or intravenously. The results following intravenous administration of bile or bacteria demonstrate that systemic toxicity of bile is not a likely cause of the bile-induced increase in mortality rate. Plasma volume loss into the peritoneal cavity has been considered to be of primary importance as a cause of death in bile peritonitis[11]. However, this mechanism is also unlikely to play an important role because the accumulation of peritoneal fluid was moderate and initially as large with bile alone as that following bile and bacteria, and also because the blood pressure was not affected to a degree that would explain the differences in mortality rate. The possibility that bile directly enhances bacterial growth is unlikely since experiments *in vitro* have failed to demonstrate any effect of bile acids on the growth of *E. coli* (Reference 18 and authors' own unpublished data).

Thus, it appears that bile is noxious either by causing increased absorption and/or production of endotoxin from the peritoneal cavity or by impairing the host defence within the peritoneal cavity. Local host defences may be diminished by bile in the following ways: by a dilution effect from peritoneal exudate accumulation[19], by impaired chemotactic, engulfing or killing activities of peritoneal phagocytes (macrophages and polymorphonuclear leukocytes), by increased resistance of bile-treated bacteria to phagocytosis and/or killing, and by changes in the rate of absorption of bacteria from the peritoneal cavity.

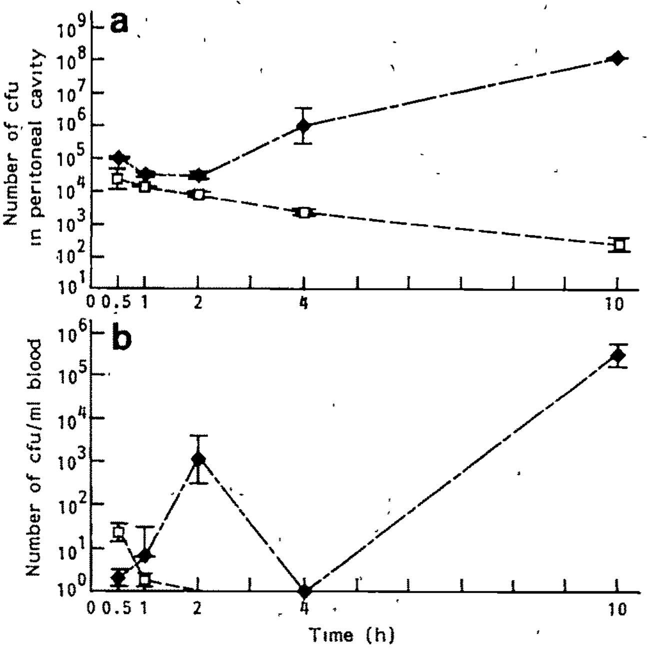

Figure 2 *Viable colony forming unit (c.f.u.) counts in* **a** *the peritoneal fluid and* **b** *the blood of rats with:* □—□, E. coli; ◆—◆, E. coli *and bile. Values are mean(s.e.m.)*

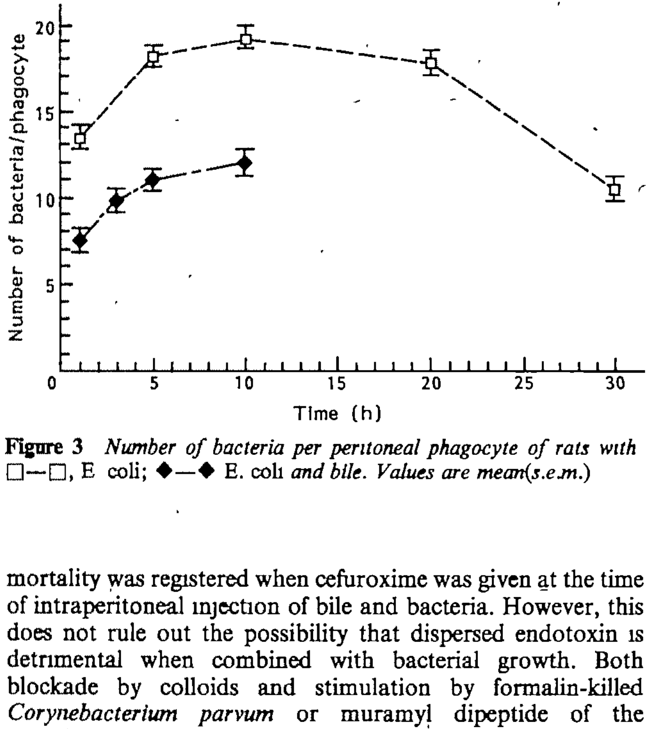

Figure 3 *Number of bacteria per peritoneal phagocyte of rats with* □—□, E coli; ◆—◆ E. coli *and bile. Values are mean(s.e.m.)*

The lipopolysaccharide cell surface component of Gram-negative bacteria is one of the most important determinants of their virulence. Detergents like bile salts may disperse lipopolysaccharides from Gram-negative bacteria[20], and this may depress local host defences in at least two ways: changes in polysaccharide structure may adversely affect bacterial uptake by macrophages[21], while liberated endotoxin may be detrimental because it leads to excessive release of biologically active mediators[22]. In the present study, no morbidity nor mortality was registered when cefuroxime was given at the time of intraperitoneal injection of bile and bacteria. However, this does not rule out the possibility that dispersed endotoxin is detrimental when combined with bacterial growth. Both blockade by colloids and stimulation by formalin-killed *Corynebacterium parvum* or muramyl dipeptide of the reticuloendothelial system have been shown to lead to an increased toxicity and mortality rate from endotoxins[23–25].

The finding of a decreased number of bacteria per peritoneal phagocyte, together with an unchanged number of peritoneal phagocytes, in rats receiving intraperitoneal *E. coli* and bile when compared with rats receiving intraperitoneal *E. coli* alone, has the following implications. It is consistent with a decreased chemotactic or engulfing ability of phagocytes. An increased ability to kill ingested bacteria in *E. coli* and bile peritonitis is also consistent with a decreased number of bacteria per phagocyte but is not consistent with the comparatively large numbers of bacteria demonstrated by viable counts in the peritoneal cavity or blood. The increased volume of peritoneal fluid in *E. coli* and bile peritonitis would act to dilute opsonins and reduce the chance of interaction between bacteria and phagocytes. However, although accumulation of intraperitoneal fluid may be a contributory factor, this does not explain the combination of an increased number of intraperitoneal bacteria and a decreased number of bacteria per phagocyte in *E. coli* and bile peritonitis. Thus, it appears that other factors, such as impaired phagocytic activity, are more important for the increased mortality rate in *E. coli* and bile peritonitis. Finally, reduced numbers of bacteria in peritoneal phagocytes might result from an increased absorption of bacteria into the blood. This remains a possibility because the bacterial growth curves in the abdominal cavity and blood are compatible with both unchanged and increased absorption (*Figure 2*). However, increased absorption into the blood cannot be the sole explanation because it does not explain the comparatively large numbers of peritoneal bacteria in rats receiving *E. coli* and bile intraperitoneally.

In summary, it appears that the increased mortality rate following intraperitoneal administration of *E. coli* and bile was due mainly to the reduced chemotactic or engulfing abilities of the peritoneal phagocytes Possibly, bile-induced accumulation of peritoneal fluid and the increased absorption of bacteria from the peritoneum into the blood may have contributed to the rapid development of sepsis. Bile may affect chemotaxis and engulfment of bacteria via a direct effect on the bacterial cell wall, by liberating endotoxin from the bacterial surface, or by inhibiting the activation of complement (C5), the binding of complement by phagocyte receptors or the phagocyte response (migration, engulfment) to the binding of complement. Some of these events may be interrelated and most of them can be explained by the detergent–lytic effects of bile salts[20,21].

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T tube intubation in the management of seriously ill patients with oesophagopleural fistulae

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Ten patients referred late with oesophagopleural fistulae were managed by T tube intubation of the oesophageal defect. Seven survived and six had radiographic evidence of closure of the defect. One patient who removed his T tube early was discharged to convalesce with a small oesophagocutaneous fistula. Three patients died as a consequence of pre-existing renal failure, upper gastrointestinal haemorrhage and adult respiratory distress syndrome. Patients presenting late with multisystem complications and ongoing sepsis secondary to oesophagopleural fistulae pose a major management problem. Our preliminary results suggest that T tube intubation offers a potential alternative to major surgical intervention, when more conservative measures have failed.

Keywords: Oesophageal perforation, T tube intubation

Patients referred within 24 h of an oesophageal perforation are best treated by primary repair with a few strictly defined exceptions, namely, disruption contained within the mediastinum or between the mediastinum and visceral lung pleura, drainage of the cavity back into the oesophagus, minimal symptoms and minimal clinical sepsis[1]. Patients referred late with ongoing pleural and mediastinal contamination pose a major management dilemma While intensive support may provide a period of transient stabilization, repeated episodes of systemic sepsis usually follow with further clinical deterioration. We report ten seriously ill patients referred over a 2-year period in whom a modified T tube intubation technique was employed as the primary mode of management

Patients and methods

Preoperative assessment

Ten patients, seven men and three women (age range 56–77 years, mean 66·8 years) were referred for further management of oesophagopleural fistulae. All had suffered repeated episodes of septic shock and other complications before referral (*Table 1*). Management before referral is detailed in *Table 2*. Five were referred following spontaneous oesophageal perforation (patients 1–5 in *Table 1*), two following failed primary repair of a spontaneous perforation (patients 6 and 7), two following instrumental perforations (patients 8 and 9) and one secondary to an anastomotic leak following oesophagogastrectomy (patient 10)

Operative management

Patients underwent thoracotomy under general anaesthesia using a double lumen endotracheal tube. All defects were located in the distal third of the oesophagus, four were lateral, four anterior and two anterolateral. A stricture distal to the oesophageal defect was excluded by digital examination. Following abscess drainage and pleural decortication, a T tube was fashioned by splitting the terminal 15 cm of a Portex (Portex Ltd, Hythe, UK) chest drain. The two limbs were inserted through the defect and into the oesophagus and stomach respectively The tube was sutured to the diaphragmatic pleura to distance it from the aorta and was brought out through the anterolateral chest wall following a segmental rib resection A feeding jejunostomy was fashioned in seven patients and one patient had a synchronous truncal vagotomy and pyloroplasty for a bleeding acute duodenal ulcer At the conclusion of the procedure, the T tube and pleural drains were connected to underwater seal drains and the patients nursed sitting upright in the intensive care unit

Postoperative management

All patients received systemic antibiotics and parenteral nutrition Nine required ventilation (12 h–12 days, mean 3·3 days) Five patients had low dose dopamine infusions ($<5\,\mu g\,kg^{-1}\,h^{-1}$) and four required full inotropic support.

Management of the T tube

The T tube was initially connected to an underwater seal drain because the oesophagus was in continuity with the cavity and the drain lumen. In the absence of a non-return valve mechanism, the lung would not have fully re-expanded Once a sealed track developed, excluding the pleural space, the T tube was connected to free drainage and progressively shortened (2–3 weeks after surgery, mean 19 days) when a track had developed and chest radiography showed a fully expanded lung The T tube was removed 21–30 days after surgery (mean 27), though two were accidentally removed by the patients themselves at 8 and 18 days

Results

Seven patients survived and six achieved closure of the oesophageal defect, as demonstrated by contrast radiography, between 26 and 60 days following insertion (mean 43 days). The patient who removed his T tube at 8 days still has a small oesophagocutaneous fistula 97 days after removal.

The majority of patients developed postoperative complications (*Table 3*). Three developed respiratory failure (two chest infections, one pleural collection), though only two required reventilation. Three developed renal failure, two requiring haemodialysis. The first had a protein-losing nephropathy secondary to amyloidosis, a serum albumin level of $19\,g\,l^{-1}$ and gross body oedema. The second had chronic renal impairment. and sepsis following premature removal of the T tube (by the patient) was the cause in the third Three developed recurrent pleural collections. Two were small and localized in patients presenting originally with multiloculated collections which may have been incompletely drained at the outset. Neither developed systemic sepsis. The only significant collection occurred in the patient who removed his T tube on the eighth postoperative day before a sealed track had developed, suffering septic shock and respiratory and renal failure as a consequence. A second patient had septic shock following feeding line contamination Two patients suffered upper gastrointestinal complications. The first perforated a benign antral gastric ulcer on the 18th postoperative day which was treated by oversew and omental patch. The second, who had originally been referred with an upper gastrointestinal haemorrhage, required two further laparotomies for duodenal

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Table 1 *Complications before referral*

Patient no.	Time from diagnosis to referral	Respiratory failure	Renal impairment	Empyema	Arrhythmias	Jaundice	Albumin ($g l^{-1}$)	Recent surgery	Other
1	48 h		Y	Y			21	Laparotomy for suspected perforated duodenal ulcer	
2	12 days	Y	Y	Bilateral	Cardiac arrest	Y	25	Cholecystectomy for gallstones	
3	6 days		Y	Y			19		Gross generalized oedema
4	28 days		Y	Bilateral	Atrial fibrillation	Y	25	Abdominoperineal excision of rectum for neoplasm	Upper gastrointestinal haemorrhage
5	26 h			Y			33		
6	9 days	Y	Y	Bilateral	Atrial fibrillation	Y	21	(1) Laparotomy for suspected perforated duodenal ulcer (2) Primary repair of spontaneous oesophageal perforation	
7	48 h			Bilateral			25	Primary repair of spontaneous oesophageal perforation	
8	48 h		Y	Y			24	Endoscopy and subsequent perforation	
9	48 h		Y	Y			32	Endoscopy and subsequent perforation	
10	30 days	Y	Y	Bilateral	Atrial fibrillation		23	Oesophagogastrectomy for oesophageal neoplasm	Tension pneumothorax, subhepatic and subphrenic collections

Y, yes

Table 2 *Management before referral*

	No. of patients
Intravenous fluids	10
Systemic antibiotics	10
Chest drainage	
Unilateral	4
Bilateral	4
Aspiration only	2
Parenteral nutrition	4
Ventilation	3
Inotropic support	3
Dopamine ($<5 \mu g kg^{-1} h^{-1}$)	4

Table 3 *Postoperative complications*

Cardiorespiratory	
Cardiac arrhythmias	4
Respiratory failure	3
Cardiac failure	1
Renal	
Renal failure	3
Sepsis	
Recurrent chest collections	3
Chest infection	3
Septicaemic shock	2
Upper gastrointestinal tract	
Perforated gastric ulcer	1
Gastrointestinal haemorrhage	1
Peritonitis	1

ulcer bleeding and for peritonitis following jejunostomy catheter dislodgement.

Three patients died (47, 16 and 3 days after surgery). The first had established renal failure on admission and, despite 44 days of haemodialysis and albumin infusions, his renal function and albumin levels never improved. A histological diagnosis of amyloidosis was made and dialysis discontinued. The second patient died after a complicated postoperative course from a further gastrointestinal haemorrhage. Autopsy revealed intrahepatic metastases from his rectal primary. The third death occurred in a 57-year-old alcoholic who was admitted in a moribund condition following spontaneous oesophageal perforation. He died 3 days after operation from adult respiratory distress syndrome. During follow-up (3–15 months) no survivor has complained of dysphagia and all manage a normal diet.

Discussion

T tube intubation was introduced by Abbott *et al.*[2]. Our method has the advantage of simpler construction and the capacity for progressive shortening before removal. It could be argued that splaying of the cut ends might result in distraction and enlargement of the perforation. This theoretical possibility has not in our practice caused any problems, possibly because the drain becomes softer after insertion. We have reserved T tube intubation for critically ill patients with multisystem problems following a period of conservative management, or for those with rapid clinical deterioration despite intensive support. Patients presenting within 24 h of perforation are managed by primary repair, while patients presenting with instrumental perforation and who fulfil Cameron's criteria[1] are managed conservatively The fundamental problem in the seriously ill patient is repeated systemic sepsis from ongoing pleural and mediastinal contamination from oesophageal secretions and gastro-oesophageal reflux, which is an important factor in delaying the healing of the oesophageal defect[3] In such patients, thoracotomy is indicated for pleural and mediastinal toilet. It adds little to the operation time to insert a T tube, which has the added advantage of providing a track for drainage of oesophageal secretions and gastro-oesophageal reflux material to the exclusion of the pleural space. This reduces the risk of systemic sepsis, but it is imperative that a sealed track be allowed to develop before T tube withdrawal. The importance of this is borne out by the major complications suffered by the patient who removed his T tube at 8 days. It has been suggested that, because the oesophagus has a marginal artery and lacks a mesentery, the use of the T tube would ensure that the defect would not heal[4]. Our results and the experience of Abbott *et al* [2] show this belief to be unfounded.

There is no consensus as to the best management in patients such as ours and comparison with other techniques is difficult Reports tend to contain small case numbers, patient subgroups are heterogeneous and include some referred early with those referred late, and the results of radical surgery do not always detail the mortality rate associated with secondary reconstruction. Primary repair is generally inadvisable[4], though selected patients have been successfully treated[5–11]. A radical surgical approach employing oesophageal exclusion and diversion is advocated by Urschel and others[3,4,11], though this approach has the theoretical disadvantage of creating a distal obstruction which might promote drainage of mucus and microorganisms through the perforation[12] and also requires the patient to undergo two major procedures. Conversely, a more conservative approach has been recommended[13] where a thoracotomy permits mediastinal and pleural toilet and accurate drain placement.

In conclusion, we do not accept that in the absence of a distal stricture all defects will heal by drainage alone. In selected cases a policy of pleural and nasogastric drainage supplemented by parenteral nutrition and antibiotics is warranted. This paper deals with the rapidly deteriorating patient with gross pleural sepsis and its attendant sequelae. Drainage of the mediastinal and pleural collections undoubtedly contributes to patient stabilization, but there remains the fundamental problem of the underlying oesophageal defect. In the past we have advocated pleural drainage in patients referred late[14] but, because of the rapidity of clinical stabilization achieved with T tube intubation, we would conclude that the T tube has a place in the armamentarium of those faced with this most difficult problem

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Oesophageal manometry and pH recording does not predict the bad results of Nissen fundoplication

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A prospective study of the value of preoperative oesophageal manometry in selecting patients for gastro-oesophageal reflux surgery has been performed. One hundred and twenty-six consecutive patients had a floppy Nissen fundoplication with a median follow-up period of 48 months (range 21–96 months). Reflux was controlled in 116 patients (92·1 per cent). One hundred and five patients (83·3 per cent) had a clinically satisfactory result (Visick grades 1 and 2). Poor results were largely due to recurrent reflux, technical failure or the irritable bowel syndrome. An unsatisfactory result was not more likely in those with upright reflux, an oesophageal motility disorder or a competent cardia as defined by manometry. Preoperative oesophageal studies, other than those required to make an accurate diagnosis, were found to have no value in deciding the suitability of patients for surgical correction of gastro-oesophageal reflux.

Keywords: Nissen fundoplication, oesophageal manometry, oesophageal pH recording

The Nissen fundoplication is probably the most commonly performed operation for gastro-oesophageal reflux. A small randomized prospective study has suggested that it might be superior to both the Belsey and the Hill operations for reflux control[1]. However, complete 360° fundoplication has a reputation for being complicated by troublesome dysphagia and gas bloat in up to a quarter of cases[2,3]. In addition, many physicians and surgeons remain sceptical of the value of reflux surgery in general, and reports of new operations continue to proliferate.

The incidence of side-effects following Nissen fundoplication may be reduced if a 'floppy' fundoplication is performed as described by Donahue and Bombeck[4,5]. It has been suggested that side-effects can be reduced still further if oesophageal manometry and 24-h pH recording are performed before operation to identify a high-risk group of patients[6,7]. DeMeester[7] has stated that surgery should be avoided in three groups of patients, namely those with reflux which occurs only in the upright position, those with a severe motility disorder, and those with a 'competent' cardia as judged by manometry.

Oesophageal function studies, particularly oesophageal manometry, require a considerable investment of capital, time and expertise. They are also uncomfortable to perform and if required routinely before reflux surgery this would be seen as a disadvantage.

A properly constructed Nissen fundoplication is considered to be a simple and effective solution to the problem of intractable gastro-oesophageal reflux. Extensive preoperative evaluation, other than that required for diagnosis, is not usually required. We present a prospective study of the possible value of preoperative oesophageal manometry and 24-h pH recording in selecting patients for anti-reflux surgery.

Patients and methods

Between July 1979 and September 1985, 126 consecutive patients (69 men and 57 women) with a median age of 50 years (range 21–71 years) underwent floppy Nissen fundoplication for intractable gastro-oesophageal reflux. All underwent full oesophageal function testing beforehand. The median follow-up period was 48 months (range 21–96 months). The diagnosis of gastro-oesophageal reflux was confirmed by endoscopy and 24-h pH recording. Energetic treatment with a variety of medications, including combinations of high doses of H_2 antagonists, alginate/antacid preparations, bethanechol and metoclopramide, was used for a minimum of 6 months before surgery was suggested. Most patients had had symptoms for several years before surgery (median 57 months, range 7–366 months) and had taken multiple medications during this time. The only indication for surgery was failure of vigorous medical treatment to relieve symptoms. In deciding whether an operation should be performed, no account was taken of the pattern of reflux demonstrated by pH recording, measurements of the length and pressure of the lower oesophageal sphincter, or the presence of any particular oesophageal motility disorder.

At operation the short gastric vessels were divided to mobilize the fundus of the stomach. A loose 360° fundoplication was performed around a 50 Fr mercury bougie as described by Donahue and Bombeck[4,5]. Care was also taken to produce a short (2–3 cm) wrap. The following concurrent procedures were performed: highly selective vagotomy (six cases), vagotomy and pyloroplasty (three cases), and cholecystectomy (three cases). Splenectomy was required in two cases (1·6 per cent) for intraoperative trauma. A thoracic approach was used if oesophageal shortening was suspected, for example, in patients with a large irreducible hiatus hernia or those with a severe peptic stricture.

Oesophageal manometry

All patients underwent oesophageal manometry before operation at the same session as 24-h pH recording. Manometry was performed using standard low compliance equipment. A commercially available multilumen catheter (Arndorfer Medical Specialities, Greendale, Wisconsin, USA) with an external diameter of 4 mm was used throughout. It had a central large channel (1·6 mm diameter) and eight smaller channels (0·8 mm diameter) for pressure measurement. The catheter was perfused with water from an Arndorfer pneumohydraulic pump at a rate of 0·6 ml/min. Pressure recordings were made from three radially spaced lumens 5 cm from the catheter tip and from two additional side holes at 5 cm intervals.

The lower oesophageal sphincter pressure (LOSP) was measured by a station pull-through method. This has been previously found to be superior to the rapid pull-through method and its accuracy and reproducibility has been reported from this laboratory[8]. Briefly, the difference between gastric and oesophageal pressure was calculated from the mean of ten, preferably consecutive, end-expiratory pressures at the level where maximum end-expiratory pressure was recorded. Separate measurement was made from each of the three recording channels and the LOSP was taken as the mean of the 30 values thus obtained. Results were expressed in mmHg. The length of the lower oesophageal sphincter was also recorded, as well as its relationship to the pressure inversion point, to determine its functional intra-abdominal component.

Motility in the body of the oesophagus was analysed as previously described[9]. This involved a detailed assessment of resting motility and

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the response to wet and dry swallows. The motility of the entire length of the oesophagus was studied in a leisurely fashion to allow time for abnormalities to be detected.

Oesophageal pH measurement

Until 1982, 24-h pH recording was performed in hospitalized subjects with a gastric pH electrode (Radiometer, Crawley, UK, type GK 282/c) connected to a pen chart recorder. Thereafter, recordings were taken in ambulant subjects using a miniature solid state digital recorder (Ormed, Welwyn Garden City, UK). Traces were analysed as suggested by Johnson and DeMeester[10].

High-risk groups

The following high-risk groups proposed by DeMeester were identified.

Competent cardia: LOSP >5 mmHg, intra-abdominal length >1·5 cm, and/or overall lower oesophageal sphincter length >2·5 cm

Upright reflux: no reflux in the supine position during 24-h recording

Motility disorder: severe disorder of peristalsis with more than 50 per cent of swallows producing non-propagated contractions

It should be noted that DeMeester has not been specific about what constitutes a significant motility disorder. This difficulty is discussed in the results section.

Postoperative assessment

Following operation all patients were interviewed at regular intervals and a check endoscopy performed 6–9 months after operation. One-hundred and five patients (83·3 per cent) agreed to have postoperative 24-h oesophageal pH recording. Those who did not have pH studies had a barium swallow and meal. However, all patients with residual symptoms had 24-h studies performed so that the postoperative pH results, if anything, give a slight overestimate of the proportion of failed operations.

Clinical results were assessed by modified Visick grading as follows: grade 1, asymptomatic; grade 2, minor symptoms not interfering with life or requiring medication, grade 3, residual symptoms interfering with lifestyle or requiring continuous or frequent medication, grade 4, complete failure to improve symptoms. At all follow-up visits specific leading questions were asked about residual reflux symptoms, dysphagia, abdominal bloating, diarrhoea and other abdominal or chest pain. By using detailed specific questioning it was hoped to counter the known tendency of patients to be over-optimistic about their symptoms at postoperative visits. Visick grades were assigned without prior knowledge of the preoperative manometry and pH studies to avoid intergroup bias.

Failure of reflux control was defined as persistent oesophagitis or abnormal reflux demonstrated by pH study or radiology.

Statistical methods

Possible differences between groups were assessed by the χ^2 test.

Results

One-hundred and sixteen patients (92·1 per cent) had their reflux controlled by the operation. Overall, 105 patients (83·3 per cent) had Visick grades 1 and 2 (*Table 1*). Minor symptoms, such as dysphagia or a sensation of postprandial fullness were common, but were rarely volunteered by the patient and were only discovered by specific leading questions. Twenty-one patients (16·7 per cent) had an unsatisfactory result. The reasons for the poor results are listed in *Table 2*.

Recurrent reflux and dysphagia were the most common reasons for symptomatic failure. Two of the cases of dysphagia were clearly attributable to technical factors in producing an unduly tight hiatus. Both patients required a further operation to correct the problem. Two other patients had dysphagia for different mechanical reasons. In the remaining two patients no clear explanation could be found for the dysphagia. Both had minor disturbances of motility amounting to no more than a slight increase in the frequency of tertiary contractions.

Table 1 *Overall clinical results*

Visick grade	Number
1	67 (53·2)
2	38 (30·1)
3	6 (4·8)
4	15 (11·9)

Values in parentheses are percentages

Table 2 *Cause of poor result (Visick 3 and 4)*

Predominant symptom	Number of patients	Cause
Reflux	7	Disrupted fundoplication
Dysphagia	2	Overtightened hiatus
	2	Possible motility disorder
	1	Slipped Nissen
	1	Migration of fundoplication into chest
Gas bloat	1	Aerophagy
Chest pain	2	Motility disorder
	1	Post-thoracotomy pain
Abdominal pain	3	Irritable bowel syndrome
Steatorrhoea	1	Postvagotomy

Table 3 *Results in 'high-risk' groups*

	Visick grade			
Group	1	2	3	4
All patients	67 (53·2)	38 (30·1)	6 (4·8)	15 (11·9)
Competent cardia	59 (51·7)	35 (30·7)	6 (5·3)	14 (12·3)
Upright reflux	23 (53)	14 (33)	2 (5)	4 (10)
Motility disorder	8 (57)	2 (14)	2 (14)	2 (14)

Values in parentheses are percentages

Four patients had a persistent motility disorder causing chest pain or dysphagia despite good reflux control. One patient developed intractable gas bloat, probably owing to continuous aerophagy. One who had a highly selective vagotomy developed steatorrhoea despite having normal pancreatic function after operation. Finally, one patient had persistent post-thoracotomy neuralgia.

Table 3 lists the clinical results in the three high-risk groups proposed by DeMeester. The term 'motility disorder' covers such a broad range of abnormalities that we have recorded in this table only those with a severe propulsive disorder. In these patients more than 50 per cent of swallows produced non-propulsive contractions. There were no statistically significant differences between these groups.

Clearly there may be some methodological differences between laboratories which may affect measurements of sphincter pressure. It will be seen that the majority (90·5 per cent) of our patients had a 'competent' cardia. This may question the validity of direct comparison of our values for the LOSP with those of DeMeester's group. We compared the results using two additional sets of criteria for LOSP characteristics. A 'fully competent' cardia was defined as an LOSP >5 mmHg, with a total length >2·5 cm and an intra-abdominal length >1·5 cm. A 'supercompetent cardia' had an LOSP >10 mmHg, total length >2·5 cm and an intra-abdominal length >1·5 cm. *Table 4* lists the results analysed in this way. There were still no significant differences in outcome.

In *Table 5* we have shown the outcome in patients with different types of motility disorder. These results are consistent with our previous studies in which we have found that symptoms attributable to abnormal oesophageal motility are usually helped by treating any associated gastro-oesophageal reflux[9].

Discussion

Since our only indication for anti-reflux surgery was persistence of severe symptoms despite prolonged high-dose medication,

Table 4 *Influence of increasing lower oesophageal sphincter competence*

	Visick grade			
Group	1	2	3	4
All patients	67 (53·2)	38 (30·1)	6 (4·8)	15 (11·9)
Incompetent lower oesophageal sphincter	8 (67)	3 (25)	0 (0)	1 (8)
Competent cardia	59 (51·7)	35 (30·7)	6 (5·3)	14 (12·3)
'Fully competent' cardia	19 (43)	17 (39)	3 (7)	5 (11)
'Supercompetent' cardia	11 (38)	12 (41)	3 (10)	3 (10)

Values in parentheses are percentages

Table 5 *Effect of motility disorders*

	Visick grade			
Group	1	2	3	4
All patients	67 (53·2)	38 (30·1)	6 (4·8)	15 (11·9)
Normal motility	16 (53)	10 (33)	1 (3)	3 (10)
Non-peristaltic contractions	8 (57)	2 (14)	2 (14)	2 (14)
Spasm	10 (42)	10 (42)	1 (4)	3 (13)
Damped peristalsis	18 (51)	8 (23)	2 (6)	7 (20)

Values in parentheses are percentages

we felt quite justified in breaking the recommendations of other authors regarding case selection for operation. By doing so we have demonstrated that there are no easily defineable risk factors that indicate a group of patients who are particularly prone to develop postoperative problems following Nissen fundoplication.

There may be several reasons for these contradictory results. Firstly, some reports may have concerned technically unsatisfactory operations[3], in which, for example, a fundoplication is constructed that is too tight or too long. There is no information on this subject, but Henderson[11] has suggested that a technically unsatisfactory fundoplication may lead to problems. In such circumstances, patients with poor motility are likely to have the most dysphagia. This should not be the case with a properly constructed floppy fundoplication which is inherently non-obstructive.

Secondly, it is possible that other workers have used less stringent criteria for adequate medical management. If this is done more patients with a low pain threshold or other gastrointestinal problems may be subjected to operation with inevitably poor results. Such problem patients are likely to have a competent cardia or upright reflux since they will, by definition, not have severe stigmata of reflux disease.

Finally, there may be minor differences in surgical technique or manometric assessment, but none is obvious to us at present. We therefore offer the reassurance that Nissen fundoplication may be safely performed in those patients who are genuinely refractory to vigorous medical treatment regardless of the subtleties of preoperative manometry or pH recording.

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Achalasia-like syndrome in systemic sclerosis

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Two methods of quantifying oesophageal emptying for liquids have been used to assess the dysphagia of patients with systemic sclerosis: the oesophageal infusion scintiscan and the timed Gastrografin® swallow. Upper gastrointestinal endoscopy and oesophageal manometry were also performed. Thirteen patients with oesophageal symptoms were studied. Eight had dysphagia, and all of these had endoscopies with no evidence of oesophagitis or stricture. Four of these eight subjects had gross delay of oesophageal emptying for fluids, and manometry showed absence of oesophageal peristalsis and incomplete relaxation of the lower oesophageal sphincter. This abnormality is similar to achalasia. Two of these four patients have benefited from pneumatic dilatation with improvement in their severe dysphagia. We believe that pneumatic dilatation should be considered in patients with systemic sclerosis and severe dysphagia where reflux oesophagitis is not apparent.

Keywords: Achalasia-like syndrome, systemic sclerosis, oesophageal function tests

Authors of early isolated reports of oesophageal involvement in patients with systemic sclerosis commented on the occurrence of marked delay in oesophageal emptying on radiography[1–3]. Oesophageal strictures were not found and 'cardiospasm' was considered to be responsible for the dysphagia. Since the 1940s studies have shown that oesophageal involvement is common, affecting up to 90 per cent of patients[4].

Oesophageal manometric abnormalities include low pressure peristalsis mainly in the distal half of the oesophagus, aperistalsis and low pressure at the lower oesophageal sphincter[5,6]. Oesophagitis and stricture formation can occur in up to 45 per cent of patients due to gastro-oesophageal reflux[7]. Strictures and weak or absent peristalsis have been thought to be the main explanation for dysphagia associated with systemic sclerosis[5], although cardiospasm has also been a considered mechanism[1–3].

However, we observed that severe dysphagia and delay in oesophageal emptying may be present in the absence of oesophagitis or strictures. This study was designed to elucidate the reasons for dysphagia in patients with systemic sclerosis, using the four different diagnostic methods of upper gastrointestinal endoscopy, oesophageal manometry, timed Gastrografin® (Schering Health Care Ltd., Burgess Hill, UK) swallow and oesophageal infusion scintiscan.

Patients and methods

Subjects

Thirteen patients (12 women, one man, median age 40 years, range 32–62 years) with systemic sclerosis were studied (group 1) All patients fulfilled the American Rheumatism Association's criteria for systemic sclerosis[8] Inclusion criteria for the study required the patients to have oesophageal symptoms including either dysphagia or heartburn (*Table 1*). Patients 1–8 complained of dysphagia, and three of these patients also had heartburn Seven normal subjects without gastrointestinal symptoms or symptoms of Raynaud's phenomenon (five women, two men; median age 43 years, range 22–46 years) acted as controls (group 2) for the oesophageal emptying studies. One other control subject was recruited for the study but was found later to suffer from Raynaud's phenomenon and was not included in the final analyses.

Upper gastrointestinal endoscopy

Standard upper gastrointestinal endoscopy under intravenous sedation was carried out on all 13 patients with systemic sclerosis.

Oesophageal manometry

Oesophageal manometry was performed on 11 patients with systemic sclerosis A six-lumen polyvinyl chloride oesophageal manometry catheter was passed in the fasting state Three distal orifices were axially positioned at 120° and proximal orifices were spaced at 5 and 10 cm. Sterile water was perfused using a low compliance syringe pump (Harvard Apparatus Company, Massachusetts, USA) at a constant rate of 2 ml/min, and measurements were transmitted via a pressure transducer and displayed on a three-channel recorder (Bryans Autograph 6®, Gould Bryan Instruments Ltd., Mitcham, UK) The tube was passed into the stomach to determine the baseline intragastric pressure and gradually withdrawn to locate the lower oesophageal sphincter The sphincter orifice showing the greatest sphincter pressure was used to assess sphincter relaxation during swallowing Thereafter continuous pressure recordings were made of the proximal and distal oesophagus and of the lower oesophageal sphincter, including responses to ten 5-ml swallows. Peristaltic contractions were defined as weak when they were less than 20 mmHg, and lower oesophageal sphincter relaxation as incomplete if on relaxation the pressure was still 5 mmHg or more above the baseline.

Oesophageal emptying tests

Timed Gastrografin swallow This test was performed on each patient and control subject and involved two consecutive swallows of 15 ml Gastrografin (10 per cent weight volume sodium diatrizoate) in the standing position. The time was measured for the Gastrografin to clear the lower oesophagus from the moment of initial laryngeal movement, as judged by radiographic screening. The Gastrografin was considered to be cleared when no fluid column remained and only a fine mucosal coating was seen.

Oesophageal infusion scintiscan Oesophageal emptying was also assessed by a new infusion scintiscan method developed by the authors

Table 1 *Characteristics of patients and control subjects*

	n	Age (years)*	Sex (F/M)	No. of patients with dysphagia	No. of patients with heartburn
Patients (group 1)	13	40 (32–62)	12/1	8	8
Controls (group 2)	7	43 (22–46)	5/2	—	—

X Values are median with range in parentheses

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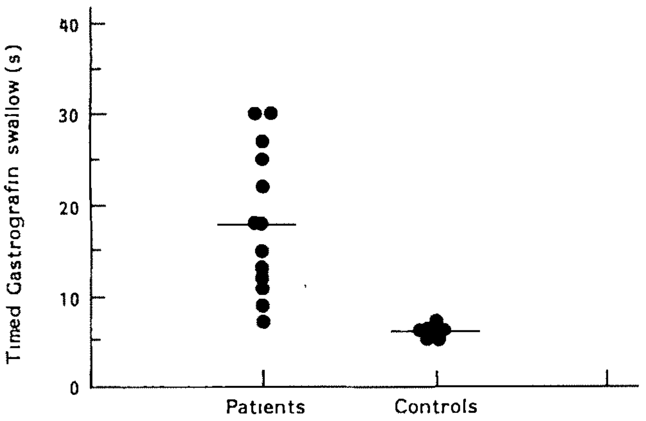

Figure 1 *Results of timed Gastrografin swallows in control and patient groups Horizontal bars represent median results*

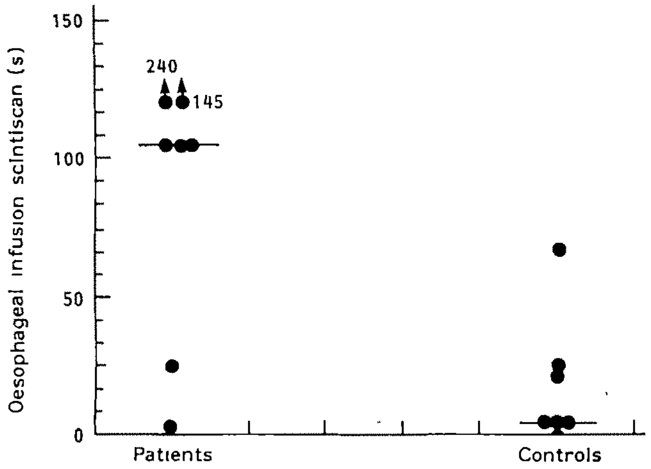

Figure 2 *Results of the oesophageal infusion scintiscan in control and patient groups. Horizontal bars represent median results*

Results were obtained for eight patients and all the controls. This method excluded swallow variability between subjects. Studies were performed using a large field-of-view camera fitted with a low energy all-purpose collimator and interfaced to a microcomputer. Patients sat in front of the γ camera, tilted back 45° from the horizontal. A fine-bore plastic catheter was placed in the oesophagus, the tip lying approximately 30 cm from the incisor teeth, 50 ml water containing 40 MBq ^{99m}technetium-labelled colloid were infused via the catheter over 25 s Imaging began at the onset of infusion. One-second images were obtained for the first 30 s and then 5-s images for 4·5 min All the data were stored on computer for subsequent analysis. An area of interest was drawn around the oesophagus The percentage of the total administered counts remaining within this area was calculated for each image. For the purposes of this study the time required for 95 per cent of the dose to leave the oesophagus was calculated

Statistical analyses

Comparisons between the patient and control groups were made using the Wilcoxon rank sum test Analyses of the results of the two methods of oesophageal emptying were performed by calculating the Spearman's rank correlation coefficient Results were considered to be significant if $P<0{\cdot}05$.

Results

The results for the upper gastrointestinal endoscopies, oesophageal manometry and the oesophageal emptying tests on the patients are summarized in *Table 2*

Upper gastrointestinal endoscopy

Only three patients were found to have endoscopic abnormalities and, in particular, only two patients had evidence of oesophagitis. At endoscopy no patient had food residue in the oesophagus and only patient 7 had a patulous cardia.

Oesophageal manometry

Satisfactory manometric recordings were obtained from all 11 patients on whom these measurements were made. Four patients were found to have both aperistalsis and incomplete sphincter relaxation.

Timed Gastrografin swallow

The timed Gastrografin swallow (median, range) was significantly delayed in the patient group (18 s, 7–30 s) compared with the control group (6 s, 5–7 s) ($P<0{\cdot}01$) (*Figure 1*). A further 14 controls had timed Gastrografin swallows only, and showed values of 7 s or less.

Oesophageal infusion scintiscan

There was a significant delay in the oesophageal emptying assessed by the oesophageal infusion scintiscan (median, range) between group 1 (105 s, 0–240 s) and group 2 (4 s, 0–67 s) ($P<0{\cdot}05$) (*Figure 2*). The eight patients who complained of dysphagia had very prolonged oesophageal emptying times as assessed by the two emptying tests (*Table 2*) There was good correlation between the two oesophageal emptying tests ($r_S=0{\cdot}66$, $P<0{\cdot}01$) (*Figure 3*).

Discussion

Symptoms of heartburn, chest pain and dysphagia are commonly encountered in patients with systemic sclerosis. Atkinson and Summerling found that 13 of 22 patients with the disease had symptoms of gastro-oesophageal reflux and only five patients complained of dysphagia[5]. We were surprised to find that eight of 13 patients (62 per cent) who complained of troublesome dysphagia were found to have no stricture or oesophagitis on endoscopy. This does not appear to be the result of bias in patient selection. Other studies have confirmed the high incidence of dysphagia in patients with systemic sclerosis: Hamel-Roy *et al.* found that 13 of 15 patients had troublesome dysphagia[9], and the problem was also found in six of nine patients investigated by Schneider *et al.*[10].

Previous oesophageal scintigraphic studies have demonstrated delayed oesophageal transit and delay in emptying in these patients[11,12]. The two tests used in this study, the timed Gastrografin swallow and the oesophageal infusion scintiscan, also demonstrated significant delay, which was more marked in patients with dysphagia. We believe the oesophageal infusion scintiscan is a better indicator of delay in emptying since it excludes any swallow variability, especially delay in the initial stages of swallowing. The timed Gastrografin swallow allows only a semiquantitative estimation of delay However, there is good correlation between the two tests ($r_S=0{\cdot}66$, $P<0{\cdot}01$) (*Figure 3*). The timed Gastrografin swallow offers an inexpensive, easy assessment of delay in oesophageal emptying. Although oesophageal manometry was used by Tolin *et al.*[11], this study is the first to document results for manometry, endoscopy and scintigraphy. The present study clearly demonstrated that stricture was not the cause of the delay. Moreover eight of the patients had a barium meal examination around the time of the study without demonstrating an oesophageal stricture. In four patients the oesophagus was described as being dilated.

The measurement of pressure in the lower oesophageal sphincter is beset with problems. Firstly, where pressure is measured at a point, as in infusion manometry systems, the infusion point may move either up or down in relation to the high pressure zone, and may give a false impression of sphincter relaxation by moving into an area of lower pressure. The use of a Dent sleeve may help to solve this problem[13]. Secondly, pressure in the zone, even when measured using a 5-cm Dent sleeve, varies considerably throughout the interdigestive cycle; this is readily seen if there is continuous pressure measurement

Table 2 *Results of upper gastrointestinal endoscopy, oesophageal manometry and oesophageal emptying tests in patients with systemic sclerosis*

		Oesophageal manometry			Oesophageal emptying tests	
Patient no	Endoscopic appearance	Peristalsis	Lower oesophageal sphincter pressure (mmHg)	Sphincter relaxation	Oesophageal infusion scintiscan (s)	Timed Gastrografin® swallow (s)
1	Hiatus hernia	Aperistalsis	15	Incomplete	240	25
2	Normal	Aperistalsis	30	Incomplete	105	18
3	Normal	Aperistalsis	10	Incomplete	145	18
4	Normal	Aperistalsis	0	–	–	11
5	Normal	Aperistalsis	15	Incomplete	–	22
6	Normal	Aperistalsis	8	Complete	–	11
7	Normal	Weak	10	Complete	–	30
8	Normal	Weak	0	–	105	30
9	Mild oesophagitis	–	–	–	0	7
10	Mild oesophagitis	–	–	–	105	27
11	Normal	Weak	16	Incomplete	3	13
12	Normal	Aperistalsis	0	–	–	9
13	Normal	Aperistalsis	0	–	25	12

Normal lower oesophageal sphincter pressure is 15–25 mmHg

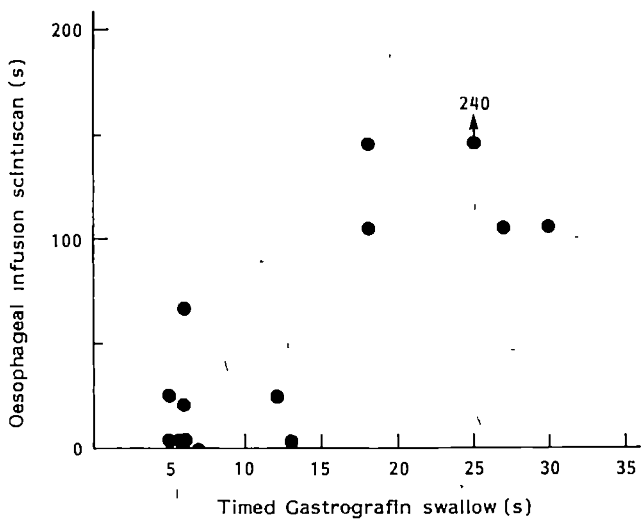

Figure 3 *Correlation between the results of timed Gastrografin swallows and the oesophageal infusion scintiscan tests in 15 subjects* ($r_S=0{\cdot}66$, $P<0.01$)

over hours. For these reasons a precise sphincter pressure should not be quoted unless the precise time relationship to oesophageal peristalsis and gastric interdigestive activity is noted It is, however, easy to recognize incomplete relaxation of the lower oesophageal sphincter, and this finding must always be significant – a pressure higher than zero at any point between the lower oesophagus and stomach can be seen as a potential barrier to flow.

The finding of incomplete relaxation of the sphincter and aperistalsis in this study was present in four of the patients (patients 1, 2, 3 and 5). Three of these patients (patients 1, 2 and 3) also had gross delay in oesophageal emptying according to two independent tests, the oesophageal infusion scintiscan and the timed Gastrografin swallow. Patient 5 did not have a scintiscan but her swallow test was prolonged. Another four patients (patients 4, 6, 12 and 13) had aperistalsis in response to swallow and normal sphincter relaxation or indiscernable sphincter pressure. These latter four patients had no delay in oesophageal emptying as assessed by the emptying tests. This suggests that poor sphincter relaxation is a more important cause of delayed oesophageal emptying than absent contraction in the oesophageal body.

Four of the patients with dysphagia had manometric findings of both aperistalsis and incomplete lower oesophageal sphincter relaxation and gross delay in oesophageal emptying similar to those of achalasia. Hamel-Roy *et al* noted incomplete relaxation of the lower oesophageal sphincter in 11 patients with systemic sclerosis, and some patients also had aperistalsis[9]. Oesophageal emptying was not measured in their patients. Although early reports suggested that achalasia might be associated with the delay in oesophageal emptying in patients with systemic sclerosis, later reports using manometry and pharmacological testing of the lower oesophageal sphincter did not confirm this. In fact, the response of the sphincter to mecholyl was diminished compared with the exaggerated response found in achalasia[5,14]. From this study we have demonstrated a group of systemic sclerosis patients with dysphagia who have an achalasia-like syndrome. Two patients in this group who had severe dysphagia and gross delay in oesophageal emptying have required intervention with oesophageal pneumatic dilatation. This treatment has produced relief of dysphagia without recurrence 23 and 24 months after dilatation. One patient had a small post-dilatation oesophageal perforation which was treated conservatively.

We suggest that management of these patients with dysphagia should not be limited to anti-reflux methods and that pneumatic dilatation should be considered in patients with non-stricture dysphagia. It is not known whether the lower oesophagus in patients with systemic sclerosis is more susceptible to perforation during balloon dilatation. Post-mortem studies have shown that the smooth muscle in the lower oesophagus can be partially replaced by fibrous tissue[2,5]. In view of this potential risk, careful observation is recommended after dilatation. The development of reflux oesophagitis after dilatation of the lower oesophagus does occur. The severity of dysphagia in our two patients was such that they both accepted this risk. Subsequently neither has had more than mild heartburn, although further follow-up is required.

In conclusion, we have shown an unexpectedly high incidence of an achalasia-like syndrome in systemic sclerosis.

Acknowledgements

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An aid to aortic aneurysm surgery

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We describe a simple technique which has proved to be of assistance during abdominal aortic aneurysm surgery. The inlay technique of aneurysm repair described by Creech[1] is considered by many to be the optimum in both elective and emergency surgery Its advantages include minimal dissection with less chance of blood loss caused by damage to lumbar vessels. The posterior layer of the proximal anastomosis presents the most demanding part of this operation. The posterior wall of an aneurysm has two main anatomical variants, either smooth or ridged; a posterior ridge, when present, facilitates suturing. However, an estimated 10–15 per cent of cases are flat, which makes retrieval of the needle tip and enclosure of an adequate bite of aortic wall within the suture difficult.

Methods

After the aneurysm sac is opened, any lumbar vessels which are back-bleeding are undersewn An aneurysm needle, Semb clamp or similar instrument is gently passed behind the aorta at the level of the proposed proximal anastomosis A silicone rubber rod (Silastic®, Dow Corning, Reading, UK) 25 cm long and 4 mm in diameter, such as is used in rectal prolapse repair[2], is drawn through behind the aorta. Traction on the rod raises a false ridge in the posterior aortic wall Traction can be maintained by the application of clamps to either end of the rod, thereby maintaining the ridge without extra assistance. Sutures are passed, from within the proximal aortic lumen, behind the rod (*Figure 1*) It is not important whether the rod is transfixed. 2/0 Prolene® (Ethicon Ltd., Edinburgh, UK) is used as the suture material, as a heavy suture may be less likely to cut out. When the posterior layer is complete, the Silastic rod under light tension is trimmed flush with the aorta and retracts well away from the duodenum.

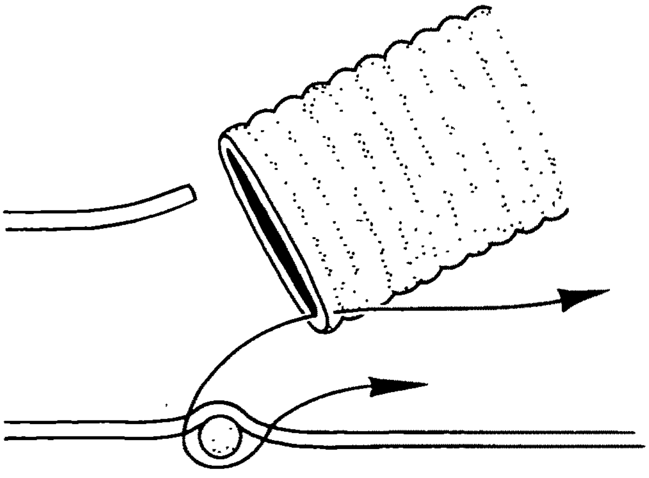

Figure 1 *The path of suture through the graft, into the posterior aortic wall and behind the Silastic rod, shown by the arrows*

Discussion

The Silastic rod has been used in this unit for several years without any technical problem. If endarterectomy of a heavily calcified aorta is required, the sling is particularly useful, as it can reinforce a friable posterior wall and prevent sutures from cutting out. Anastomotic stenosis has not been observed and there has been no evidence of infection or fistula formation. No immediate or long-term complications which could be ascribed to the technique have occurred.

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Total gastrectomy and oesophagojejunostomy – a prospective randomized trial of hand-sutured *versus* mechanically stapled anastomoses

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Eighty patients undergoing total gastrectomy for malignant disease were entered into a prospective randomized study, comparing anastomoses constructed mechanically (staples) with hand-sewn (single layer Maxon®) anastomoses. The groups were matched with respect to clinical features, medical risk factors and were staged for tumour. Only one anastomotic leak was observed after operation and this was in the group of stapled anastomoses. One patient died in each group (owing to cardiac infarction and multiorgan failure). Operating time, morbidity and hospital stay showed no significant differences between groups. These results indicate that hand-sewn and mechanically stapled oesophagojejunostomy anastomoses allow the same high standard of performance.

Keywords: Total gastrectomy, oesophagojejunostomy, stapled anastomosis, hand-sewn anastomosis

There is no definitive study comparing oesophagojejunostomy carried out by stapling devices with hand-sewn anastomoses. Previous studies were either not randomized[1] or compared prospectively collected data for the use of staples with historical hand-sewn controls, which usually gave a disportionately high failure rate[2]. Improvements in suturing techniques and materials used have allowed improvement in the results of hand-sewn anastomoses, making previously described failure rates of around 15 per cent[3,4] no longer appropriate.

The aim of this study was to evaluate differences in anastomotic leakage, morbidity, mortality and operating time, comparing stapled with hand-sewn anastomoses.

Patients and methods

Eighty patients undergoing elective total gastrectomy and intra-abdominal oesophagojejunal anastomoses were randomized to reconstruction by hand-sewn (M) or stapled (S) anastomoses In each case, an end-to-side oesophagojejunal anastomosis was carried out using a Roux-en-Y jejunal segment of at least 60 cm in length.

Hand-sewn anastomoses were performed using a single row of 4/0 USP absorbable sutures (polyglyconate, monofilament, Maxon®, Davies and Geck, Wayne, New Jersey, USA) without an enveloping jejunoplication, with the blind end of the loop being closed with a TA-55 stapler (United States Surgical Corporation, Norwalk, Connecticut, USA) Stapled anastomoses used the curved EAA instrument with size 25 staples (United States Surgical Corporation, Norwalk, Connecticut, USA). The purse-string suture was placed using the ASP-50 clamp and the distal oesophagus dilated with the measurement gauge or a dressing forceps. The EEA device was introduced above the blind end of the small intestine

In each anastomosis the integrity was checked intraoperatively by distension with fluid or air, even if staple doughnuts were complete The blind end of the jejunal loop was shortened in each patient using a TA-55 stapler (United States Surgical Corporation, Norwalk, Connecticut, USA)

Other technical details were identical in each group. resection of the greater and lesser omentum, closure of the duodenum with a straight staple line with reinforcing sutures when necessary, splenectomy (except in patients with an antral tumour or during palliative procedures), lymphadenectomy in surgery with a curative goal, and the use of the GIA and TA staplers for the proximal jejunum

Nasogastric intubation was discontinued after 24 h, except if large quantities of secretions were aspirated, when it was removed on the fifth day, at which time anastomotic integrity was checked using the water-soluble contrast medium Gastrografin® (Schering AG, Berlin, FRG).

Technical problems, operative time and postoperative complications were documented up to the 30th day or up to the time of discharge if this was longer If clinical suspicion of anastomotic leakage occurred, then radiological examination was repeated

Statistical analysis was carried out using the Wilcoxon, the Mann–Whitney U test and the χ^2 tests

Patient characteristics

Between February 1987 and July 1988, 80 patients were studied in two groups These two groups were well matched with respect to age, number and nature of previous operations and risk factors (diabetes, hypertension, cachexia, etc., *Table 1*). In group S two patients had undergone previous partial gastrectomy, one 16 years ago for duodenal ulceration and another 2 years earlier for gastric carcinoma In group M one patient had undergone partial gastrectomy previously for distal gastric ulceration

The main indication for surgery was adenocarcinoma in 70 patients, lymphoma in nine patients and leiomyosarcoma in one patient The classification of the gastric neoplasms, the extent of the primary tumours or lymph node status was not different between the two groups (*Table 2*) Potentially curative surgery was carried out in 64 per cent of the patients; this required excision of neighbouring organs in 18 per cent of patients in group M and 20 per cent of those in group S. (*Table 3*)

Results

Operative time did not differ significantly between groups, even allowing for differing time between surgeons Stapled anastomoses saved about 15 min over hand-sewn anastomoses but this was not reflected in a statistically significant reduction of total operating time.

Intraoperative complications occurred in six patients in group S. Anastomotic leakage was apparent in three patients and these were immediately oversewn. In one of these patients a further leak developed 8 days after operation (*Table 4*) which closed spontaneously after a further week without complication. One intraoperative technical failure occurred when on opening the ASP-50 purse-string clamp the threads caught and tore the oesophagus longitudinally A further resection was carried out and the anastomoses were hand-sewn. Two further longitudinal tears of the oesophagus occurred using a Bougie for dilatation. These leaks were oversewn immediately and neither led to further problems.

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Table 1 *Patient characteristics*

	Total ($n=80$)	M ($n=40$)	S ($n=40$)
Median age (range)	62 (25–78)	61 (42–75)	63 (25–78)
Male	44 (55)	18 (45)	26 (65)
Previous operations*	22 (28)	12 (30)	10 (25)
Concomitant disease†	31 (39)	15 (38)	16 (40)

M, hand-sewn anastomoses, S, stapled anastomoses Values in parentheses are percentages * Appendicectomy, cholecystectomy, bowel resection, partial gastrectomy, gynaecological operations and pancreaticojejunostomy † Obesity, atherosclerosis, coronary heart disease, pulmonary disease, cachexia, diabetes mellitus and hypertension

Table 2 *Tumour characteristics*

	Total ($n=80$)	M ($n=40$)	S ($n=40$)
Carcinoma	70 (88)	36 (90)	34 (85)
Malignant lymphoma	9 (11)	3 (8)	6 (15)
Leiomyosarcoma	1 (1)	1 (2)	–
Carcinoma type (Lauren)			
Intestinal	24 (30)	13 (33)	11 (28)
Diffuse	41 (51)	21 (53)	20 (50)
Mixed cellularity	5 (6)	2 (5)	3 (8)
Carcinoma staging			
Early cancer	16 (20)	9 (23)	7 (18)
T1–T3	62 (78)	28 (70)	34 (85)
T4	18 (23)	12 (30)	6 (15)
N0–N2	68 (85)	32 (80)	36 (90)
N3	12 (15)	8 (20)	4 (10)

M, hand-sewn anastomoses; S, stapled anastomoses Values in parentheses are percentages

Table 3 *Characteristics of operation*

	Total (n=80)	M ($n=40$)	S ($n=40$)
Potentially curative	51 (64)	21 (53)	30 (75)
Splenectomy	52 (65)	26 (65)	26 (65)
Extension of operation*	15 (19)	7 (18)	8 (20)
Median operating time in minutes (range)	187 (85–340)	194 (85–340)	180 (90–270)

M, hand-sewn anastomoses, S, stapled anastomoses Values in parentheses are percentages * Bowel resection, pancreatic resection, adrenalectomy, liver resection, resection of diaphragm

The only late complication in group M was a transient anastomotic stenosis which resolved spontaneously.

The difference in the rate of immediate and late failures between group S (six of 40 patients) and group M (one of 40 patients) was not statistically significant.

Other postoperative complications are summarized in *Table 5*. Two patients died, one of a cardiac infarction 1 week after operation and the other from acute necrotizing pancreatitis 30 days after operation. The anastomoses in these patients were intact at autopsy The incidence of other complications was similar in both groups, ranging from pleural effusion to intra-abdominal abscess, and 8 per cent of patients required further laparotomy for bleeding, adhesions, ileus and a left subphrenic abscess.

Hospital stay ranged from 8 to 92 days without differences between the two groups (*Table 5*). Eight patients died from malignant disease in the follow-up period, but to date clinical and radiological follow-up has not revealed anastomotic stenoses in any patient.

Discussion

Stapled anastomoses are said to save operating time and allow greater reliance upon the anastomosis, resulting in reduced morbidity and shorter hospital stay The use of stapled anastomoses in anorectal surgery has confirmed some of these advantages (shortened operation time) and has allowed the development of continence-preserving surgery in one-fifth of men[5,6]

Uncontrolled studies of the use of stapled anastomoses in oesophagojejunostomy have shown some advantages[1,7] and Ulrich and Kochel[2] reported a reduction of clinically apparent anastomotic leakage from 13·6 per cent to 5·1 per cent. The patients with hand-sewn anastomoses, however, were obtained as historical controls, some being operated upon 20 years previously. Another non-randomized study alleged reduction in anastomotic leakage from 29 per cent to 13 per cent with the use of a stapled anastomoses, with a concomitant reduced mortality rate from 26 per cent to 3 per cent[1].

Anastomotic leakage from hand-sewn anastomoses should not exceed 10 per cent, and improved results may be due to the technique of enveloping the anastomosis with intestinal serosa[8]. Our results, using a one-layer anastomosis, and others in the literature for two-layer anastomoses (1 per cent leakage, 2 per cent mortality[9]), are probably related to the optimal exposure of a generous transverse laparotomy with extension in the midline up to the xiphoid process. The abdominal oesophagus becomes so accessible that the anastomosis can be readily carried out by hand or stapler. Oesophageal dilatation is best carried out using dressing forceps and the purse-string is probably best placed manually with the suture no more than 2 mm from the cut oesophageal edge. These steps facilitate the stapled anastomosis.

The potential advantages of the stapled anastomosis (less trauma of the intestine[7], uniform suture tension and reduced impairment of intestinal blood flow[10,11]) do not appear to be of decisive importance for adequate anastomotic healing.

The incidence of complications was high (41 per cent) in both groups and could have been due to the relatively high mean age of the patients, linked with the extent of the surgery Sepsis

Table 4 *Secondary complications of oesophagojejunostomy*

	Total ($n=80$)	M ($n=40$)	S ($n=40$)
Insufficiency	1	0	1
Transient stenosis	1	1	0
Bleeding	0	0	0

M, hand-sewn anastomoses S, stapled anastomoses

Table 5 *Postoperative course*

	Total (n=80)	M ($n=40$)	S ($n=40$)
Median hospital stay in days (range)	17 (8–92)	18 (9–92)	16 (8–60)
General complications			
Death	2	1	1
Pleuropulmonary	15	6	9
Intra-abdominal abscess	5	1	4
Duodenal stump insufficiency	5	3	2
Pancreatic fistula	5	2	3
Bleeding (intra-abdominal)	3	1	2
Wound infection	3	1	2
Others*	9	3	6
Patients with complications	33 (41)	14 (35)	19 (48)
Relaparotomy	6 (8)	2 (5)	4 (10)

M, hand-sewn anastomoses, S, stapled anastomoses Values in parentheses are percentages. * Bowel obstruction, cholecystitis, thrombophlebitis, colon perforation within the abdomen and the wound occurred equally in both groups, calling into question the allegation that stapled anastomoses reduce contamination[6]. Greater lengths of intestine and oesophagus remain open during stapled anastomoses but for a shorter time than hand-sewn segments A shortened anastomotic time agrees with measurements with animal experiments[10], but this did not reduce total operative time in group S. The high costs of the stapler are therefore not defrayed by a shortening of operative time or by reduced morbidity, hospitalization time or mortality. Manually placed sutures remain crucial to reinforce any stapled anastomotic leaks and the hand-sewn technique must not be neglected during surgical training.

This prospective study shows that the use of a stapled anastomosis does not increase the reliability of the anastomosis and does not reduce the total operating time The complication rate and lengths of hospital stay are the same between patients undergoing stapled or hand-sewn anastomoses. One advantage of a stapled anastomosis is that it allows more radical surgery of a proximal gastric carcinoma without thoracotomy, especially with tumours demonstrating intramural infiltration[12]

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Early and late results of extended surgery for cancer of the stomach

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The experience of the Istituto Nazionale Tumori of Milan of 143 patients who underwent extended surgery for cancer of the stomach from 1965 to 1980 is reviewed. They represent 16·3 per cent of the patients who underwent curative surgery. The operative mortality rate was 15·4 per cent but this significantly decreased in recent years to 8 per cent and the morbidity rate to 17·5 per cent. The overall 5-year survival rate was 19 per cent. Survival was analysed according to tumour penetration (pT) and nodal status (N). It was found that patients without tumour penetration of adjacent structures and nodal involvement (pT3N−) had a better 5-year survival rate (21 per cent) than patients with nodal involvement (pT3N+) (2 per cent). Patients with tumour penetration of adjacent structures and without nodal involvement (pT4N−) had a better 5-year survival rate (29 per cent) than patients with nodal involvement (pT4N+) (5 per cent). These differences were significant on log rank test ($P<0\cdot000001$ and $P<0\cdot001$ respectively) and suggest that nodal status is a stronger prognostic variable than pT level. The role of extended surgery is discussed from the viewpoint of the oncological surgeon who has to weigh up the difficulty of a preoperative diagnosis of tumour infiltration of adjacent structures (predictive positive value 0·39), with the operative mortality rate of at least 8 per cent and long-term results which are strongly affected by the nodal status.

Keywords: Gastric cancer, extended surgery

Local invasion of surrounding structures and organs is a frequent occurrence in patients with gastric cancer, the reported incidence ranging from 10 to 23 per cent[1–4]. The surgeon who is faced with a locally advanced gastric cancer has to assess during the operation the benefit to risk ratio of extended surgery, often without having a precise knowledge of the microscopical neoplastic invasion of the adjacent organs

We have reviewed our experience with extended surgery for lesions of the stomach with suspected invasion of neighbouring tissues with particular reference to tumours classified as pT3 (penetration through the serosa without invading contiguous structures) or pT4 (lesions with involvement of immediately adjacent tissues and organs) according to the TNM classification[5], and have analysed our data in terms of operative morbidity and mortality rates and long-term results.

Patients and methods

From 1965 to 1980, 876 patients underwent curative surgery (proximal subtotal gastrectomy, distal subtotal gastrectomy and total gastrectomy) for gastric cancer at the Istituto Nazionale Tumori of Milan. In 143 patients (16·3 per cent) other organs or structures had been removed in association with proximal subtotal gastrectomy (56 patients), distal subtotal gastrectomy (50 patients) and total gastrectomy (37 patients) Neoplastic invasion of the adjacent structures was suspected during surgery in 72 patients In the remaining 71 patients resection of the stomach in conjunction with other organs was undertaken because of technical problems at operation, the presence of inflammatory adhesions, the choice of a '*de principe*' extended operation or causes which could not be assessed by retrospective analysis

Microscopic invasion of adjacent structures was confirmed by the pathologist in only 28 of the 72 patients (39 per cent) with suspected neoplastic invasion (even in the presence of firm adhesion to the primary tumour) and in 19 of the 71 patients (27 per cent) resected for other reasons.

The distribution of patients according to sex, age, histological tumour type, type of surgery, depth of invasion of the gastric wall and nodal status in relation to microscopic invasion of adjacent structures is shown in *Table 1* Radical extended surgery involved the following structures: spleen ($n=104$), pancreas ($n=65$), liver ($n=14$), colon ($n=13$), mesocolon ($n=4$), left adrenal gland ($n=4$), gallbladder ($n=2$), intrathoracic oesophagus ($n=2$), ovary ($n=2$), kidney ($n=1$) and diaphragm wall ($n=1$). Sixty-three of these patients needed excision of more than one structure at the time of stomach excision (*Table 2*).

The standard gastrectomy performed at this institute consists of removal of all or part of the stomach together with neighbouring organs and lymph nodes of the second level if neoplastic invasion of these structures is suspected Removal begins with detachment of the greater omentum from the transverse colon from right to left, the anterior leaf

Table 1 *Main clinical and pathological variables in patients undergoing extended gastric surgery*

	Microscopic invasion of adjacent structures		
	Absent	Present	No of cases
No. of patients	96	47	143
Male/female ratio	71/25	32/15	103/40
Median age (years)	62·8	61·3	—
Histological type			
Intestinal	63	33	96
Diffuse	26	11	37
Mixed	7	3	10
Type of surgery			
PSG	40	16	56
DSG	29	21	50
TG	27	10	37
Invasion of the gastric wall			
pT2	11	–	11
pT3	85	–	85
pT4	–	47	47
Nodal status			
N_0	28	13	41
N_1	40	17	57
N_2	15	8	23
N_3	6	3	9
Unknown	7	6	13

PSG, proximal subtotal gastrectomy, DSG, distal subtotal gastrectomy; TG, total gastrectomy

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Table 2 *Surgical procedures performed*

Resected organs and/or structures	Proximal subtotal gastrectomy (*n*=56)							Distal subtotal gastrectomy (*n*=50)				Total gastrectomy (*n*=37)							Total (*n*=143)
Multiple organs	39	(32	3	1	1	1	1)	6	(4	1	1)	18	(10	2	1	2	2	1)	63
Spleen	13	X	X	X	X	X	X	13	X			18	X	X	X	X	X		44
Pancreas	1	X	X			X	X	10	X		X	1	X					X	12
Liver	1			X		X		8		X		–				X			9
Colon	–		X					8				–		X					8
Mesocolon	–							3			X	–							3
Oesophagus	2							–				–							2
Gallbladder	–							1				–						X	1
Left adrenal gland	–		X					–		X		–							–
Ovary	–							–				–					X		–
Kidney	–							1				–							1
Lung	–				X			–				–							–
Diaphragm	–							–				–			X				–

The ordinal numbers indicate the numbers of patients who had surgery extended to other organs, multiple or single, beyond the stomach X indicates the organs resected in patients with multiple organ resection, the numbers of which are reported in the first line within brackets

Table 3 *Morbidity rate in relation to resected organs*

Organs and/or structures	*n*	%	Subphrenic abscess	Fistula	Peritonitis	Peptic oesophagitis	Miscellaneous†
Spleen	7	16	2‡	2‡	1‡	1‡	1
Spleen and pancreas	11	22	4‡	4‡		1‡	2
Pancreas	3	25	1‡		1‡		1
Colon	2	15	1‡				1
Oesophagus	1	50					1
Miscellaneous*	1	5					1
Total	25	17	8‡	6‡	2‡	2‡	7

* Including spleen and lung; † bronchopulmonary infection, wound infection

of the mesocolon is removed with the omentum The right gastroepiploic vessels are ligated and divided at the inferior margin of the pancreas The lesser omentum is detached from under the surface of the left lobe of the liver, and the anterior leaf of the hepatoduodenal ligament is divided down to the origin of the right gastric vessels which are divided and ligated When total gastrectomy or distal subtotal gastrectomy is planned, the duodenum is divided and the distal stomach (including omentum, suprapyloric, infrapyloric and peripancreatic lymph nodes) is lifted out of the left margin of the incision The left gastric vessels are then isolated and ligated, and lymph nodes along the lesser curvature and along the left gastric artery are removed If total gastrectomy is planned, dissection continues normally with clearance of right and left sides of the cardia. The stomach is then resected and reconstruction is performed by gastrojejunostomy or an end-to-side or end-to-end Roux-en-Y oesophagojejunostomy.

If proximal subtotal gastrectomy is planned, the left gastric vessels are isolated and the ascending branch is ligated, lymph nodes along the lesser curvature and left gastric artery are removed The dissection and lymphadenectomy continue cranially to the cardia. The right gastroepiploic vessels are not ligated The stomach is then resected and reconstruction is performed by end-to-side oesophagogastrostomy. The removal of the stomach and neighbouring structures or organs (pancreas, spleen, mesocolon, transverse colon, diaphragm, liver, gallbladder and oesophagus) is generally performed *en bloc*.

Gastric carcinomas were classified according to Lauren's classification, which comprises intestinal, diffuse and mixed types The depth of the gastric wall invasion and pT stage were scored according to the TNM criteria and nodal involvement was assessed microscopically On the basis of the histological examination of the resected specimen, subtotal and total gastrectomies were categorized as 'absolute or relative curative' or 'relative non-curative' resections by the criteria of the Japanese Research Society for Gastric Cancer[6]. Absolute non-curative resections (those with evidence of residual cancer) are not considered in this report

Survival rates were calculated by the product limit approach as suggested by Kaplan and Meier[7], considering only the patients who survived the operation. The significance of differences in survival curves were tested by the log rank test

Table 4 *Mortality rate in relation to resected organs*

Resected organs	*n*	Operative mortality rate *n* (%)
Spleen	44	8 (18)
Spleen and pancreas	51	9 (18)
Pancreas	12	2 (17)
Miscellaneous	36	3 (8)
Total	143	22 (15·4)

Results

This series represents 16·3 per cent of all patients operated on for gastric cancer at the Istituto Nazionale Tumori of Milan, and for 28·8 per cent of those who underwent a radical surgical procedure. Data regarding morbidity and mortality rates according to the organs resected and mortality rate according to the type of surgery are shown in *Tables 3–5* The overall in-hospital mortality rate was 15·4 per cent but this rate decreased from 28 per cent to 12 per cent to 8 per cent over the years 1965–1970, 1971–1975 and 1976–1980 respectively. No clear relationship was found between the mortality rate and the type of organ resected *en bloc* with the stomach or the type of gastrectomy performed, with the exception of resection of the spleen or pancreas which was associated with a higher mortality rate than surgery extended to other organs or structures.

Table 5 *Mortality rate in relation to type of surgery*

Surgical procedure	Mortality rate n (%)	Cause of death
Proximal subtotal gastrectomy, $n=56$	10 (18)	Fistulas, 4; shock, 2, pleural emphysema, 1; peritonitis, 1; haemorrhage, 1, pulmonary embolism, 1
Distal subtotal gastrectomy, $n=50$	7 (14)	Haemorrhage, 3; fistulas, 2, pancreatitis, 1; pulmonary embolism, 1
Total gastrectomy, $n=37$	5 (14)	Peritonitis, 2, fistula, 1; pancreatitis, 1; pulmonary embolism, 1

Table 6 *Intraoperative evaluation and histopathological confirmation of neoplastic involvement of resected structures*

	Infiltration	
Organs resected	Clinical (n)	Histological n (%)
Spleen	11	1 (9)
Spleen and pancreas	33	10 (30)
Pancreas	9	3 (33)
Liver	9	5 (56)
Colon	6	5 (83)
Oesophagus	2	2 (100)
Gallbladder	2	2 (100)
Total	72	28 (39)

The relationship between the clinical assessment of neoplastic invasion and microscopic involvement is reported in *Table 6* The positive predictive value of the clinical judgement of neoplastic infiltration was higher in the case of involvement of hollow viscera than of parenchymal organs.

The 5-year survival rate is shown in *Figure 1*. The overall 5-year survival rate was 19 per cent and the vast majority of patients developed recurrence during the first 2 or 3 years after the operation. Survival was also analysed according to tumour penetration (pT) and nodal status (N). It was found that patients classified as pT3N− had a better survival rate than those graded as pT3N+ ($P<0.000001$), and those classified as pT4N− did better than pT4N+ ($P<0.001$). Thus, in groups of patients with similar extent of invasion of the gastric wall, nodal status significantly affected the prognosis. However, when patients were compared within homogeneous groups for nodal invasion, no significant difference was apparent between pT3N− and pT4N−, or pT3N+ and pT4N+. This suggests that nodal status is a stronger prognostic variable than pT level

These findings are consistent with data reported in *Table 7* which shows the failure rate according to the state of the resected organs Numbers are too small to define a different risk of failure according to involvement of different organs, and in general the recurrence rate is only slightly higher in patients classified as pT4 than in those as pT3.

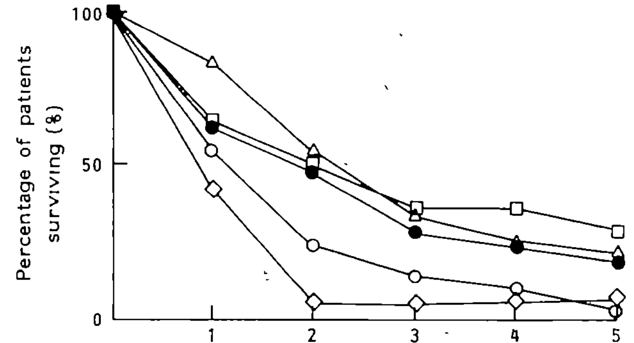
Analysis of the failure rate according to the site of the primary tumour was not performed because of the small number of patients, and the literature reports that there is no difference in survival rate when comparing carcinoma of the lower-middle and upper-third of the stomach with N_0 and N_1 lymph node metastases[8] or cancers located in the upper region with those involving the lower and middle regions[9].

Discussion

Three points deserve consideration. First, the surgeon faced during the operation with the necessity of extending the resection to adjacent organs because of clinical suspicion of infiltration should be clearly aware that his judgement will be correct in about one-third of cases This should prompt careful intra-abdominal exploration and sampling of suspected areas of invasion for microscopic frozen section analysis, especially when suspicion rests on parenchymal organs where clinical assessment is less precise and biopsy less dangerous than in the case of hollow viscera.

Second, we consider that the current operative mortality rate of 8 per cent is acceptable and compares favourably with figures of 14–21 per cent reported in other Western countries[3,10] even if it is still far from the figure of 3 per cent reported by Japanese authors[2,4]. Since infections and anastomotic leakages account for the majority of lethal complications, it is our opinion that the drop in our mortality rate observed in the last period may reflect some improvement in intraoperative management (use of staplers) and perioperative management with liberal use of total parenteral nutrition[11] It is our contention that paying more attention to intraoperative technique, proper use of drains and appropriate selection of prophylactic antibiotics may help to reduce further the operative mortality rate.

Finally, the long-term results are obviously dismal when compared with the figures obtained following conventional operations for less advanced malignancies[12,13]. However, both the median and 5-year survival rates are better than those obtained following absolute non-curative resection[14] or following radical surgery for other malignancies such as pancreatic cancer, where an 8 per cent 5-year survival rate is commonly accepted[15].



Numbers of patients at risk		1	2	3	4	5
pT3 N−	△ 24	20	13	8	6	5
pT4 N−	□ 14	9	7	5	5	4
pT3 N+	○ 42	23	10	6	4	1
pT4 N+	◇ 19	8	1	1	1	1

Figure 1 *Survival of patients with and without neoplastic invasion of the resected structures and nodal involvement* ●—●, *overall* (n=*99*), □—□, *N− with neoplastic invasion* (n=*14*), △—△, *N− without neoplastic invasion* (n=*24*), ◇—◇, *N+ with neoplastic invasion* (n=*19*); *and* ○—○, *N+ without neoplastic invasion* (n=*42*) *Excluded from the analysis are 44 patients* (*22 postoperative deaths, 13 nodal status unknown, 9 follow-up incomplete*)

Table 7 *Number of recurrences according to additional organ or structure excised*

	With infiltration		Without infiltration	
Resected organ	No. of patients, n	No of failures, n (%)	No. of patients, n (%)	No of failures, n (%)
Spleen	1	1 (100)	30	15 (50)
Spleen and pancreas	9	4 (44)	25	8 (32)
Pancreas	3	2 (67)	5	2 (40)
Colon	5	3 (60)	3	1 (33)
Mesocolon	3	1 (33)	–	– (–)
Liver	4	1 (25)	3	1 (33)
Oesophagus	2	1 (50)	–	– (–)
Diaphragm	–	– (–)	1	1 (100)

Table 8 *Five-year survival rate after resection of the stomach and invaded adjacent organs*

	Organ resected and survival rate (%)				
Author	Mesocolon	Spleen	Liver	Pancreas	Colon
Maruyama[16]	38·6	29·7	24·3	20·1	14·9
Papachristou and Shiu[17]					7·0
Koga *et al* [18]		31·0*			
Kishimoto and Koga[2]			50·0	21·4	12
Takagi[19]		31·3	3·7	4·7†	31·1
Takahashi[20]		29·9			
Sugimachi *et al* [21]		36·0‡			
Korenaga *et al.*[4]	43·0		25·0		35·7

* Combined splenectomy or pancreaticosplenectomy, † head of the pancreas; ‡ 4-year survival rate

An interesting question concerns the relationship between survival rate and resected organs. Our data (*Table 7*) are not strictly comparable with the 5-year survival rate reported in the literature (*Table 8*) even if the natural history of recurrent gastric cancer shows that all patients with relapse usually die within 1 year. If we analyse the recurrence rate following resection of organs microscopically involved by tumour, this appears to be higher than when the same organs are found to be free of tumour, even if the smaller number and distribution of cases precludes statistical evaluation. Analysis of the literature (*Table 8*) on this topic is intriguing: most of the data come from Japanese papers which do not state whether extended resection was performed as a consequence of microscopical invasion or not, and values of 20–36 per cent for the 5-year survival rate are reported[22].

The apparently better prognosis following splenectomy as opposed to partial pancreatectomy or colectomy could reflect the attitude whereby the spleen is removed routinely to achieve better lymphadenectomy, even though two recent Japanese studies[20,21] have documented a markedly detrimental effect on patient survival following splenectomy. In our experience no metastases (hilar or parenchymal) were found in 17 patients undergoing splenectomy for cancer of the inferior third of the stomach, while metastases were present in 8 per cent of patients with tumours of the upper or middle third of the organ. Since the morbidity and mortality rates of the added procedure are not negligible, this argues against routine splenectomy in patients with tumours of the inferior third of the stomach where nodal involvement is extremely rare (and represents distant rather than regional metastasis).

The major prognostic determinant remains, as in our previous analysis[12], the presence of nodal involvement. The coupling of two negative prognostic factors, such as an advanced tumour requiring extended surgery and lymph node involvement, resulted in a 5-year survival rate of only 2–5 per cent Especially in these cases, the surgeon must carefully weigh the benefit to risk ratio, if the operative mortality rate is low an absolute non-curative resection represents the best available palliative therapy in locally advanced cancer of the stomach[14].

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Role of pyloroplasty in the retrosternal stomach: results of a prospective, randomized, controlled trial

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A prospective, randomized, controlled trial comparing clinical outcome and emptying of a solid meal from the retrosternal stomach, with and without pyloroplasty is described. Forty consecutive patients with oesophageal cancer undergoing retrosternal gastric reconstruction of the oesophagus were studied. In 20 patients the pylorus was left intact (group 1) and 20 patients underwent an Aust[1] pyloroplasty (group 2). Nine patients in group 1 suffered postoperative symptoms of gastric stasis compared with only one patient in group 2 (P = 0·0106). Three patients in group 1 died from aspiration pneumonia before discharge from hospital. A gastric emptying test was performed on 24 patients between 1 and 3 months after surgery. By this time, most survivors had recovered from symptoms attributed to gastric stasis and no significant difference in gastric emptying could be demonstrated between the two groups. Selection of patients, a wide range of emptying times and improvement in gastric emptying on follow-up may explain the lack of correlation between postoperative symptomatology and the gastric half-emptying times. A pyloroplasty is advised to prevent the potentially lethal effects of gastric stasis in the early postoperative period following retrosternal reconstruction of the oesophagus.

Keywords: Retrosternal stomach, pyloroplasty, gastric emptying, oesophageal cancer

Most surgeons use stomach to restore gastrointestinal continuity after oesophagectomy and to bypass unresectable oesophageal cancers. The stomach may be placed in the right or left pleural cavity, in the posterior mediastinum, or behind the sternum. Truncal vagotomy delays emptying from the abdominal stomach[2], but the need for a drainage procedure on the totally vagotomized intrathoracic stomach is a controversial issue[3].

When the pylorus of the mobilized stomach is left intact, risk of leakage from an additional suture line is avoided and postprandial dumping or duodenogastric reflux may be less frequent. However, if a drainage procedure is necessary to facilitate emptying from the intrathoracic stomach, omission of pyloroplasty could lead to gastric stasis, vomiting and aspiration

In this paper, we report the results of a prospective, randomized, controlled trial to compare clinical outcome and emptying of a solid meal from the retrosternal stomach with and without pyloroplasty. The postoperative course of each patient was carefully documented, particular attention being paid to complications suggestive of abnormal gastric emptying.

Patients and methods

The study group consisted of 32 men and eight women ranging from 34 to 70 years of age (mean age 54 years) with squamous carcinoma of the thoracic oesophagus, who were admitted to Baragwanath Hospital, Johannesburg from June 1985 to December 1987 All patients underwent surgery, during which the whole stomach was placed retrosternally to reconstruct the oesophagus. Informed consent for inclusion in the trial was obtained and patients were randomly allocated to one of two groups In group 1 the pylorus was left intact and in group 2 an Aust pyloroplasty[1] was performed After a barium swallow examination on the seventh postoperative day to exclude leakage from the cervical oesophagogastric anastomosis, the patients were given oral fluids, commencing with small volumes of 100 ml/h. Semi-solids were introduced into the diet on the tenth postoperative and solid food on the 14th day Each patient was advised to eat slowly and not to lie down immediately after meals. All complications before and after discharge from hospital were recorded.

No sooner than 1 month after operation, gastric emptying of a 100 g meat meal, labelled with ^{99m}technetium–tin colloid heat-fixed to the solid, was measured[4] in the erect and supine positions. The gastric region of interest was visually defined on the oscilloscope screen of a γ camera. Activity in the retrosternal stomach was measured with anterior and posterior detectors for 60 s at 5, 10, 15 and 30 min after ingestion of the meal and at half-hourly intervals for up to 3 h. The geometric mean counts were calculated to correct for variations in depth and tissue attenuation, and all counts were corrected for decay of the technetium marker. On a second occasion, not less than 72 h after the first meal, the test was repeated with the patient in the opposite (erect or supine) position. Serial studies of emptying of the solid meal were later performed in the erect position to examine the effect of time on this function of the retrosternal stomach.

Data analysis

The time at which the patient finished the meal was designated T_0 and the highest count value in the retrosternal stomach during the first half-hour was selected as the maximum. Gastric retention at each time interval was expressed as a percentage of the maximum count value. The gastric half-emptying time ($T_{\frac{1}{2}}$) was the time taken for activity in the stomach to reach 50 per cent of the maximum count value. The results were analysed by the Wilcoxon signed ranks test and χ^2 test, with Yates' correction where necessary.

Results

The number of cases, age distribution, sex ratio and clinical staging in the two groups were similar (*Table 1*). Patients with stage 2 disease underwent oesophagectomy and an oesophageal bypass was performed for those with stage 3 disease. There were no complications relating to construction of the pyloroplasty.

Operative mortality

There were four deaths in hospital. Three patients in group 1 (stage 2, two patients; stage 3, one patient) died from aspiration

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Table 1 *Comparison of groups*

	Group 1 ($n=20$)	Group 2 ($n=20$)
Sex ratio (M:F)	4:1	4:1
Mean age (years)	52	54
Range (years)	37–68	34–70
*Stage of disease		
2	4	6
3	16	14

* American Joint Committee system of staging of oesophageal cancer

Table 2 *Postoperative symptoms in patients with a retrosternal stomach*

	Group 1	Group 2
Aspiration	4*	0
Food vomiting	1	0
Postprandial fullness	2	1
Heartburn	2	0

* Includes three patients dying from aspiration pneumonia before discharge

pneumonia, diagnosed by chest radiography showing changes compatible with aspiration and by sputum culture of enteric bacteria. One patient in group 2 with stage 3 disease died of the septic complications of an anastomotic fistula.

Postoperative morbidity

The incidence of wound infection and transient leaks from the anastomosis was similar in both groups. A total of nine patients in group 1 had symptoms of gastric stasis compared with one patient in group 2 (*Table 2*). This difference between the two groups is significant ($P=0.0106$).

Gastric emptying

Twenty-four patients, 10 in group 1 and 14 in group 2, returned after discharge from hospital for measurement of gastric emptying between one and three months after operation. The other seven survivors in group 1 eligible for, but declining, the test included three patients who had complained of postoperative postprandial fullness or vomiting. None of the five survivors in group 2 who did not undergo the test had suffered postoperative symptoms of gastric stasis. The solid meal emptied from the retrosternal stomach faster in the erect than in the supine position in both groups. In group 1 the median $T_{\frac{1}{2}}$ was 63 min (range <5 to >180 min) in the erect position and 83 min (range 6 to >180 min) in the supine position. The median $T_{\frac{1}{2}}$ in group 2 was 54 min (range <5 to 180 min) in the erect and 134 min (range <5 to >180 min) in the supine position. When the two groups were compared, no difference could be identified for emptying of the solid meal in either the erect or the supine position. No correlation could be demonstrated between postoperative symptoms of delayed gastric emptying and the percentage gastric retention of the solid meal at each time interval in either position.

Follow-up studies

The median follow-up of patients in group 1 was 8 months (range 2–26 months). At the last review, five of the six patients with postoperative symptoms of gastric stasis had recovered from them. The other patient in group 1, complaining of reflux and heartburn after surgery, was readmitted with aspiration pneumonia 2 months after discharge and died in hospital. In group 2 the median follow-up was 10 months (range 3–20 months). The patient who suffered postprandial vomiting in the early postoperative period became asymptomatic on review. Another patient in group 2 developed dumping 4 months after surgery.

Six patients in group 1 and seven patients in group 2 gave informed written consent for a second study of gastric emptying. This was performed in the erect sitting position an average of 5 months (range 1–9 months) after the first test (*Figure 1*). In group 1, no change in the erect $T_{\frac{1}{2}}$ was noted in four patients, two patients emptied two solid meals at a faster and two patients at a slower rate. Four patients in group 2 had faster gastric emptying, in two patients the erect $T_{\frac{1}{2}}$ was the same and one patient emptied the meal more slowly.

Discussion

The retrosternal route for gastric replacement of the oesophagus has several distinct advantages. Distension of the retrosternal stomach with air or fluid in the early postoperative period does not compress the lung and increase the risk of postoperative pneumonia. The retrosternal space is remote from the tumour bed and adjuvant radiotherapy can be given without fear of radiation damage to the stomach. The retrosternal stomach is unlikely to be invaded by locally recurrent tumour. Little is known about the function of the retrosternal stomach and particularly the requirement for a drainage procedure to facilitate emptying of a solid meal.

It is difficult to draw conclusions from previous studies of emptying from the intrathoracic stomach because of variation in operative technique[5–7], the route of replacement[6,7], and the nature of the test meal[8–10] or swallow[11]. There has been little agreement on the necessity for a drainage procedure and most investigators found that fluids empty rapidly from both abdominal[12] and thoracic stomachs[13] after gastric or oesophageal surgery. Patients with delayed gastric emptying were more likely to experience symptoms of gastric stasis after solid food[14]. Emptying of a solid meal was, therefore, measured in this study of the function of the retrosternal stomach.

There was a difference in the incidence of postoperative symptoms of gastric stasis between the two groups. Patients with an intact pylorus were more liable to aspiration, postprandial distress, vomiting and heartburn than those with a pyloroplasty. This difference was not only statistically significant but clinically important: a total of four patients in group 1 died from aspiration pneumonia, three before discharge from hospital and one readmitted 2 months after operation. Performance of a pyloroplasty in group 2 probably reduced gastric outflow resistance and the effects of postvagotomy gastric atony in the early postoperative period[15]. The results from group 2 are similar to those reported by Akiyama in 1980[16], where a pyloroplasty was routinely performed on the

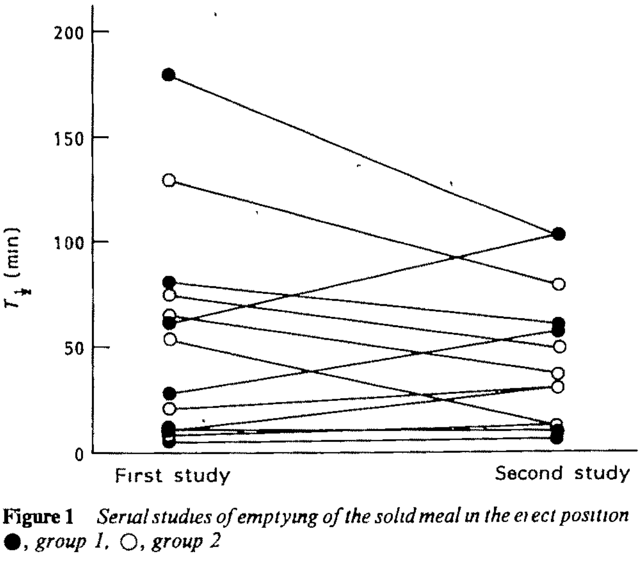

Figure 1 *Serial studies of emptying of the solid meal in the erect position* ●, *group 1*, ○, *group 2*

retrosternal stomach in 148 patients undergoing gastric bypass or reconstruction of the oesophagus; minor pulmonary complications were noted in less than 4 per cent of cases and no patient died from aspiration pneumonia.

Recurrent laryngeal nerve injury resulting in incomplete glottic closure and uncoordinated swallowing can be complicated by aspiration[16]. Routine postoperative indirect laryngoscopy was not performed on these cases and vocal cord palsy cannot be excluded. However, care was taken in each case to identify and protect the recurrent laryngeal nerves at the time of surgery and no patient was noted to be hoarse postoperatively. Recurrent laryngeal nerve injuries would, therefore, not account for the difference in incidence of aspiration pneumonia between the two groups.

The solid emptying test failed to identify a difference between the two groups and there are four possible explanations for this. The first relates to patient selection: those who died from aspiration could not undergo the test and three patients with symptoms of gastric stasis declined the study. Secondly, only a minority of patients suffer delayed gastric emptying after vagotomy[2] and the wide range of emptying makes it difficult to identify these patients when relatively few are studied. A third explanation may be related to the test meal, the small volume may limit accuracy and reproducibility of the method. Finally, there is evidence that emptying from the vagotomized stomach improves with time[10]. In this series, five of the six survivors with postoperative symptoms of gastric stasis eventually became asymptomatic, and repeat tests showed that 50 per cent of patients were emptying the solid meal at a faster rate. Emptying of a solid meal must, therefore, be measured soon after operation to correlate gastric half-emptying times with postoperative symptoms of gastric stasis.

Pyloroplasty is a simple manoeuvre and does not compromise the blood supply of the stomach. It is a safe procedure and in the one patient in group 2 who developed dumping the symptoms were easily controlled by conservative measures. A minority of patients with an intrathoracic stomach will suffer gastric stasis if the pylorus is left intact[3,10], but gastric stasis complicated by aspiration can be lethal. The 16 patients who underwent retrosternal gastric replacement of the oesophagus during 1988, therefore, had a pyloroplasty performed. There were two postoperative deaths (anastomotic leakage, *Torulopsis glabrata* septicaemia), but no patients suffered aspiration. The results of the trial and subsequent clinical experience strongly suggest that a pyloroplasty should be performed on the retrosternal stomach.

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Surgery for melanoma metastatic to the gastrointestinal tract

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Melanoma frequently disseminates to the gastrointestinal tract, being found post-mortem in 60 per cent of patients with disseminated disease, while during life it is diagnosed in only 4 per cent. During the period 1981–87, 835 melanoma patients were referred and 30 developed complaints caused by gastrointestinal metastatic melanoma. Twenty-three patients were treated surgically. The interval between treatment of the primary melanoma and detection of intestinal involvement was a median of 34 months (range 2–87 months). In four patients recurrence in the gut was the first evidence of dissemination. Major complaints were nausea and vomiting, abdominal pain, signs of anaemia, and blood in the stools. Complications were bleeding (ten cases), ileus due to intussusception (five cases), bowel perforation (four cases) and cholecystitis (one case). The metastases, mainly localized in the small bowel, were removed by relatively simple procedures. Symptoms were reduced in 19 patients. Two patients died after operation: one from sepsis due to suture leakage, the other from pneumonia and a cerebrovascular accident. Of the remaining patients, 16 survived a median of 7·5 (range 0·7–32·0) months. Five patients are still alive 72, 72, 70, 7 and 2 months after the metastasectomy, three of whom are tumour-free. The actuarial 5-year survival of all patients is 19 per cent. These results support surgical intervention for patients with complaints and/or complications attributable to gastrointestinal metastatic melanoma.

Keywords: Surgery, metastatic melanoma, gastrointestinal tract

In approximately 60 per cent of patients who die from melanoma the autopsy reveals metastases in the gastrointestinal tract. Most of these metastases are localized in the ileum and stomach, the colon being less frequently involved[1,2]. For metastases in the ileum, melanoma is considered to be the principal tumour, apart from primary tumours of the digestive tract itself[3].

Gastrointestinal metastatic melanoma occurs in several forms. The intramural nodular type is most frequently found in the stomach, and its continued growth leads to formation of polypoid masses. Ulceration of these lesions may lead to the typical radiological feature known as a 'bull's eye'. Multiple polypoid lesions are mostly encountered in the small intestine. Colon metastases are found in a variety of forms[4,5].

During life, gastrointestinal involvement is diagnosed in only 4 per cent of melanoma patients[6]. The clinician should be alerted by non-specific symptoms such as anorexia, nausea and vomiting, weight loss, signs of anaemia, melaena, periods of diarrhoea and abdominal pain, which sometimes imitate the complaints associated with peptic ulcer[7].

A striking feature can be the long interval between treatment of the primary melanoma and detection of the gastrointestinal metastases[8,9]. In most cases the diagnosis is made at a late date, when the disease is already at an advanced stage and complications have developed. The most common complications calling for surgery are bleeding (acute or chronic) and ileus due to intussusception. Bowel perforation and malabsorption are seen less frequently[10]. Surgery is performed to improve the quality of life[11]. In some instances survival after metastasectomy is reported to be very long[12].

Patients and methods

During the period 1981–87, 835 melanoma patients were referred to The Netherlands Cancer Institute. Gastrointestinal metastases were demonstrated in 30 (3·6 per cent) patients, and 23 were treated by surgery. There were 17 men and 6 women, with a median age of 44 (range 18–81) years. The primary melanoma was situated in the head–neck region in three, in the trunk in ten and in an extremity in ten patients. Clark level and Breslow thickness were known for 15 patients. The Clark level was III in three cases, IV in nine and V in three cases. The median Breslow thickness was 3·80 (range 1·5–10·0) mm. An ulcerating melanoma was seen in 13 patients at presentation. Treatment of the primary melanoma consisted of a wide excision. Adjuvant therapy was given as regional perfusion in two cases, node dissection in one and bacillus Calmette–Guérin treatment in one.

During the period preceding detection of the of the gastrointestinal metastases, local recurrences developed in two patients and regional node metastases in 16, in nine patients one or several distant metastases, at other sites, were demonstrated. In four patients the recurrence in the gut was the first sign of dissemination. The median interval between treatment of the primary melanoma and detection of the gastrointestinal metastases averaged 34 (2–87) months.

Results

The main complaints and symptoms proved to be abdominal pain, nausea and vomiting, signs of anaemia and melaena. Constipation, diarrhoea and fever were less often observed. The indication for laparotomy was acute or chronic blood loss in ten patients, ileus due to intussusception in five patients (with associated blood loss in one) and bowel perforation in four patients (with associated blood loss in three). In one patient the metastatic melanoma had given rise to cholecystitis. Three patients underwent elective surgery.

The diagnosis was made before operation in 14 patients, and during or after operation in nine patients. Diagnostic procedures were generally extensive: apart from laboratory tests for hypochromic anaemia (17 patients) and occult blood in the stools (12 patients), the following tests were performed: barium swallow (17 cases), abdominal computed tomographic scan (12), ultrasound (11), abdominal plain radiograph (eight), endoscopy (five) and selective angiography (one).

At operation, metastases were found in the ileum (seven cases), the jejunum (three), the colon (three), the omentum (one) and the gallbladder (one). In seven cases, both the small intestine and the mesentery showed tumour, the pouch of Douglas being involved once. One patient had metastases in the colon as well as in the omentum. Ten patients showed only one lesion, five showed two, and eight patients showed three

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or more lesions. Polypoid lesions were found in ten patients, and intramural nodules in two. Seven patients showed large, ulcerating tumour masses penetrating the intestinal wall and often also infiltrating the mesentery or the omentum.

The intestinal metastases were removed by bowel resection, and the gallbladder metastasis by cholecystectomy. An omentectomy was performed twice. In 13 patients the metastasectomy was considered radical; nine of these patients were free from disease at that time.

On pathological examination ulceration was seen in 19 cases, melanin was present in only nine.

After operation, one patient died from sepsis following suture leakage and one died from pneumonia, complicated by a cerebrovascular accident. Two patients developed a wound infection and one patient developed a pancreatic fistula (which closed without complication). In 18 patients (78 per cent) the postoperative course was uneventful. The median period in hospital was 15 (4–34) days The symptoms were relieved in 19 patients (83 per cent).

At the time of analysis 16 patients had died after a median survival of 7·5 (0·7–32·0) months. Five patients, all of whom were free from disease after metastasectomy, are still alive: three are tumour-free after 6 years, 6 years and 2 months respectively, and two patients have tumours after 70 months and 7 months The actuarial 5-year survival of all patients following metastasectomy is 19 per cent.

There was no relation between the duration of the relapse-free interval and the length of survival after surgical intervention.

Discussion

In the period studied, metastatic melanoma in the gastrointestinal tract was rarely diagnosed, in contrast with autopsy findings[1] which found melanoma in 60 per cent of post mortems The difference may be explained by the fact that intestinal metastases usually occur in the course of the disease when other organ systems (such as brain and lungs) are already involved. In such cases the clinical symptoms of those organs usually predominate and the intestinal symptoms tend to be non-specific.

Intestinal metastatic melanoma was diagnosed before operation in more than half of our patients, whereas in other series this was seldom the case[8,13]. However, diagnosis was often not made until an emergency occurred An awareness that the patient has had a melanoma previously treated should lead to earlier diagnosis The value of contrast radiography proved to be limited. The characteristic 'bull's eye' appearance was observed in only one case, and this is in accordance with reports in the literature[9].

As in other series[10], we found bleeding and anaemia (14 cases) to be the most common complication, which is explained by the large number of cases of ulcerating intestinal metastases. The frequent occurrence of intussusception in our series is likewise consistent with the literature[14,15], which mentions that at a more advanced age this complication is fairly often caused by a malignant process[16]. A striking feature in our series is the rather large number of bowel perforations.

Metastases were most frequently found localized in the small intestine, but often these were not polypoid as described by others[5] but large ulcerating tumour masses, infiltrating the intestinal wall and also involving the mesentery. Melanoma metastatic to the gallbladder, as was encountered in one of our patients, is very rare: the number of cases described in the literature is 13[17]. Metastatic melanoma of the stomach was not observed, but two of the patients not operated on had large gastric ulcers caused by metastatic melanoma. Since these ulcers responded well to conservative treatment, an operation was deemed unnecessary.

Polypoid lesions were observed as frequently as infiltrative lesions, which is in agreement with the literature[14]; the intramural nodule has to be regarded as an early stage of both. The mesentery can become involved in the lesion due to eccentric growth from the initially submucosal tumour deposit into the intestinal wall.

Nearly all our patients reported improvement of complaints after metastasectomy with a low postoperative morbidity rate and an acceptable mortality rate Our survival data are in agreement with those from the literature[10,18], and long-term survivals (>5 years) have also been previously reported[5,12,19]. Long-term survival is found in patients who are tumour-free after metastasectomy[20,21] Unlike others[22], we did not find a long relapse-free interval to be of positive influence on survival.

In summary, we believe that surgical treatment has to be considered for patients with complaints and/or complications of gastrointestinal metastatic melanoma. In most patients a metastasectomy can result in a satisfactory and relatively prolonged palliation.

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Short note

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Evaluation of the role of endoscopic biopsies and cytology in the detection of gastric malignancy

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The sensitivity of endoscopic biopsy ranges from 69 per cent to 99 per cent in routine clinical practice[1,2]. While multiple biopsy of gastric mucosal lesions is now standard practice, cytological analysis of smears from gastric brushings or washings is not widely performed[3]. In a prospective study, we have evaluated cytological examination in addition to endoscopic biopsy in the differentiation of benign and malignant gastric lesions.

Patients and methods

Gastric biopsy and cytological smears were obtained from 1774 consecutive patients at endoscopy, using forward viewing endoscopies with standard forceps and brushes The brushes were enclosed within an outer plastic sheath and discarded after use. The biopsies were taken before collection of the cytological smears The number of biopsy specimens taken was decided in each case by the endoscopist, and ranged between three and ten A mean of four mucosal biopsies was obtained from each patient

Cytological smears were taken using the lavage method in 615 patients, and the direct vision brushing technique in 1159 patients Washing cytology was performed using the simple lavage technique with normal saline The procedure was as follows. a No 14 Levin tube with multiple side openings was passed into the stomach which was then emptied by suction, thus obtaining the first specimen Then 250 ml normal saline were infused intragastrically, the tube was clamped and the patient was rotated several times to enable the saline to come into contact with all the gastric mucosa. This fluid was then aspirated as the second specimen. The two specimens were centrifuged and their sediments used for preparation of the smears

Where the brushing technique was performed, a nylon brush was introduced through the biopsy channel, advanced to the lesion and smears obtained by leading the brush several times across the lesion. Six smears were made on consecutively numbered slides and fixed in 95 per cent alcohol. The smears were stained using Papanicolaou's technique and processed sequentially by the same cytologist (MM) The histopathologist and the cytologist were given the same clinical information.

Results

There were no complications attributable to the endoscopic biopsies or cytological techniques. Gastric malignancy was confirmed by histopathology of the resected specimen or peroperative biopsy in 332 patients. In the resective histology, the pathologists did not specifically comment on the presence of early gastric cancer. Histological examination of the endoscopic biopsies positively confirmed gastric malignancy in 294 (89 per cent) patients (*Table 1*). Cytology demonstrated definitive evidence of malignancy in 260 (78 per cent) patients. The smears were reported as suspicious of malignant change in 17 cases (5 per cent).

Table 1 *Techniques used for positive diagnoses of gastric malignancy* (n=*332*)

Technique	Number of patients
Endoscopic biopsy	294 (89)
Cytology	260 (78)
Biopsy only	62 (19)
Cytology only	28 (8)
Biopsy with cytology	322 (97)

Values given in parentheses are percentages

Of the tumours 232 (70 per cent) were positively diagnosed both with histology and cytology. Endoscopic biopsy alone confirmed neoplastic change in 62 (19 per cent) patients. Cytological analysis confirmed the diagnosis of malignancy in 28 (8 per cent) patients, in whom multiple biopsies did not demonstrate malignant cells. Cytology showed 18 (5 per cent) false-positive reports. The cumulative diagnostic yield using both endoscopic biopsy and cytology was 322 (97 per cent) patients. Therefore, only 3 per cent of cases remained undiagnosed after simultaneous employment of biopsy and cytology.

The site of the gastric tumour did not significantly affect the diagnostic yield using either cytology or histology. However, cytology was not as useful in positively diagnosing gastric lymphoma (six of 19 patients; 32 per cent) or leiomyosarcoma (one of four patients: 25 per cent) as it was for adenocarcinoma (253 of 309 patients; 82 per cent). Using the brushing technique cytological examination had a specificity of 99 per cent compared with 97 per cent for lavage. The sensitivity of brush cytology was 76 per cent and of washing cytology 87 per cent.

Discussion

While Young and Hughes[1] reported an accuracy of 91 per cent for endoscopic cytology of the upper gastrointestinal tract, Roberts *et al.*[3] achieved only a 48 per cent positivity and suggested that this figure is probably a realistic sensitivity level to expect from a clinical cytological service. Other workers have also concluded that additional exfoliative cytology alters patient management so rarely that its routine use is of no value[4,5] Cytology combined with endoscopic biopsy markedly improved the diagnostic yield of gastric malignancy in this study, with a combined reliability rate of 97 per cent. Twenty-eight of 332 patients had their diagnosis confirmed using cytology alone. In this series the endoscopic biopsies were taken before the cytological smears A recent trial to assess whether brushing should be performed before or after biopsy concluded that smears should be taken before biopsy[6]. Adoption of this recommendation may decrease the number of false-negative reports, and an increased sensitivity may then be obtained with brushing cytology

We conclude that cytological examination of gastric mucosal smears is an important adjunct to endoscopic biopsy in diagnosing gastric malignancy, at no increased risk to the patient. If an experienced cytologist is available, cytohistological examination should be routinely performed in evaluating gastric mucosal lesions.

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Short note

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Changing pattern of distribution of carcinoma of the stomach

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Although the incidence of carcinoma of the stomach has been decreasing in recent years[1], there are several reports that tumours involving the gastric cardia are becoming more common[2–5]. Consequently, we studied the pathology records of two consecutive 6-year periods of all patients with gastric cancer operated on in our department between 1976 and 1987.

Patients and methods

During the 12-year period between 1976 and 1987, 419 patients with gastric carcinoma had an operation in the First Propaedeutic Surgical Clinic of the Athens University Patients were divided into two groups according to the year of their operation Group A comprised 122 patients operated on from 1976 to 1981, while group B consisted of 297 patients operated on between 1982 and 1987 Seventy-two patients of group A were male (59 per cent) and 50 female (41 per cent) with a mean age of 61 and 63 years respectively. In group B, 168 patients were men (56·6 per cent) and 129 women (43·4 per cent) with a mean age of 62 and 58 years

Each group was divided in to six subgroups, according to the location of the tumours: (1) cardia, tumours up to 4 cm from the oesophagogastric junction; (2) fundus, (3) body; (4) antrum, (5) cancer infiltrating the whole of the stomach; and (6) gastric stump carcinoma. If more than one tumour was found the categorization was according to the location of the largest tumour (five cases).

All tumours removed were adenocarcinomas of various degrees of differentiation. The tumours were classified according to the predominant cell types, as being poor, intermediate or well differentiated. Patients with gastric lymphomas, squamous cell carcinomas of the lower oesophagus or Barrett's oesophagus were excluded from the study

The results were evaluated statistically by the χ^2 test and Student's *t* test Values of $P<0.05$ were considered significant

Results

The distribution of tumours into the six major sites is shown in *Figure 1*. The incidence of carcinomas of the cardia was increased in group B patients (64 patients or 21·7 per cent) compared with group A (12 patients or 9·8 per cent). This difference was statistically significant ($P<0.05$) However, there was no significant change in tumour distribution in the other five subgroups studied. When tumours of the cardia and fundus are taken together there was no difference in the incidence of carcinoma between groups A and B. A considerable proportion of growths was located in the body and antrum of the stomach in both groups (group A, 65·6 per cent and group B, 63·6 per cent).

There was no difference in the incidence of tumours in various anatomical sites in the stomach, according to sex, between patients of the same group or between patients of different groups. The number of male patients was larger in all sites of the stomach, especially in the cardia The mean age of patients according to their sex and site distribution of the tumour was not found to differ between the two groups.

Tumour distribution with regard to cell differentiation showed that in tumours of the cardia there was a considerable preponderance (59 per cent) of well differentiated cell types in group B patients. However, there was no statistically significant difference in cell differentiation among the various sites in patients in the two groups (*Table 1*).

Table 1 *Tumour cell differentiation according to location in the stomach in the two groups*

	Cell differentiation					
	Group A			Group B		
Site of neoplasm	Poor *n* (%)	Intermediate *n* (%)	Well *n* (%)	Poor *n* (%)	Intermediate *n* (%)	Well *n* (%)
Cardia	4 (33)	3 (25)	5 (43)	14 (22)	12 (19)	38 (59)
Fundus	7 (35)	7 (35)	6 (30)	9 (27)	10 (30)	14 (42)
Body	21 (34)	26 (43)	14 (23)	62 (37·8)	49 (29·6)	54 (32·6)
Antrum	7 (37)	6 (32)	6 (32)	7 (29)	10 (42)	7 (29)

Group A, 112 patients; group B, 286 patients; no statistically significant differences were detected

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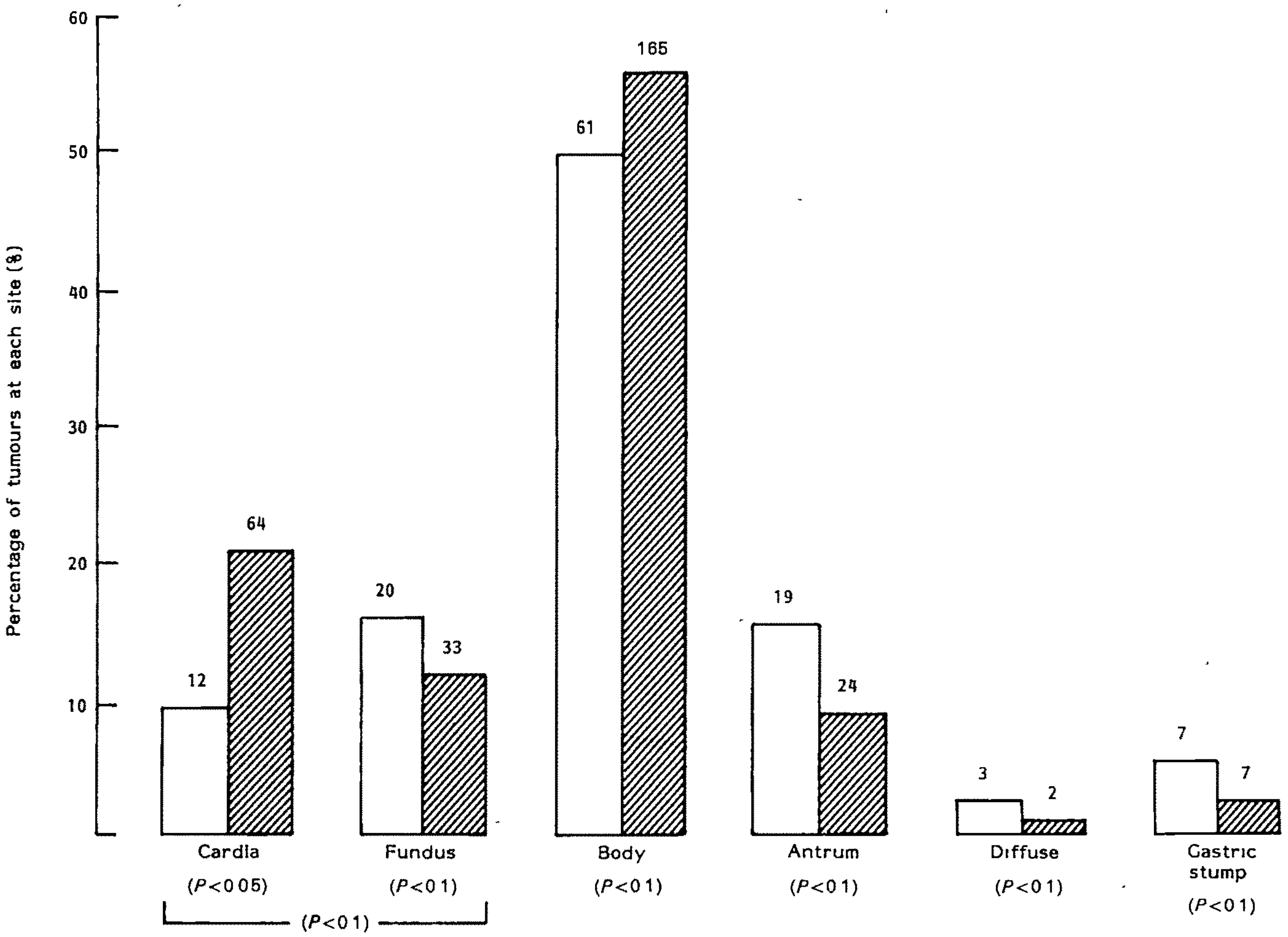

Figure 1 *Tumour distribution in the stomach of patients in the two groups* □, *group A, 1976–81,* ■, *group B, 1982–87. Numbers at the head of each column show patient numbers*

Discussion

In the present study we noted a statistically significant increase in tumours located in the cardia of the stomach, while there was no change in the distribution pattern of growths in the rest of the stomach. These findings are in agreement with reports by Papachristou *et al.*[7], Sons *et al.*[3], Paterson *et al.*[5] and Husemann[6].

The results reported by the Endoscopic Unit of our Hospital regarding the location of gastric cancer were similar during the 6-year period from its establishment (1982–87). A total of 7136 gastroscopies were performed and 361 patients with gastric cancer were detected. Among these patients 102 (28·2 per cent) had cancer of the proximal stomach, 156 (43·2 per cent) cancer of the body and 103 (28·5 per cent) cancer of the antrum.

The increase of cardia neoplasms may represent either a relative increase[3,4] or a true increase in these tumours, explained perhaps by the carcinogenic effect of cigarette smoking which affects the proximal stomach more severely[8]. The majority of our patients, especially men, were smokers. The largest proportion of smokers was found among patients with gastric cardia tumours (men 85 per cent, women 70 per cent). In contrast, only 58 per cent of patients with cancer located elsewhere in the stomach were smokers.

The reported increase of cancer of the proximal stomach is accompanied by a higher male to female ratio in certain studies[5,9]. The proportion of male patients with adenocarcinoma of the cardia was higher than in other sites of the stomach in both groups of patients but the difference was not significant. A significant difference between men and women has been reported by Antonioli *et al.*[2].

A marked difference in the histological type of the neoplasm was detected, mainly in group B patients, a well differentiated tumour being relatively common. This finding was not of statistical significance. Antonioli *et al.*[2] have demonstrated that tumours of the cardia contain signet ring cells less often, while Peterson *et al.*[5] reported an increased incidence of 'intestinal' tumours in this region. These observations on the sex ratio and pathological type support the suggestion made by Antonioli *et al.* and MacDonald *et al.*[2,9] that gastric cardia cancer and cancer of the rest of the stomach may be different diseases, and by implication require a different surgical approach.

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Highly selective vagotomy 5–15 years on

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Highly selective vagotomy for duodenal ulcer was performed on 307 patients between 1973 and 1983 without operative mortality. Of these, 283 (92·2 per cent) were followed up prospectively for a minimum of 5 years. Recurrent ulcer was diagnosed in 49 (17·3 per cent). The recurrent ulcer rate increased from 13·2 per cent at 5 years to 19·4 per cent at 12 years. Age, length of history, previous haemorrhage or perforation and preoperative acid output were not associated with increased risk of recurrent ulceration. The risk in men and smokers was higher but not significantly so. The recurrence rate for individual surgeons varied from 5·3 to 25·6 per cent. Failure of healing with H_2-receptor antagonists was not associated with a higher recurrent ulcer rate. Patients with a strong family history (more than one first degree relative affected) had a significantly higher recurrence rate (33·2 per cent at 10 years) than those without (13·5 per cent at 10 years). Of the 49 recurrent ulcer patients, 30 (61·2 per cent) required either an operation or regular H_2-receptor antagonists. Of the 250 patients (81·4 per cent) available in 1988 for review of symptoms 5–15 years after operation, 5·4 per cent had dumping, 8·9 per cent epigastric pain, and 11·8 per cent heartburn every day or most days. H_2-receptor antagonists were required by 10·7 per cent of patients on a frequent or regular basis. Of 239 patients who answered the question, 218 (91·2 per cent) felt that their symptoms had been cured or greatly improved and 203 (84·9) considered the operation a success. Despite the high recurrence rate, the operation was successful in controlling ulcer symptoms in around 90 per cent of patients and produced postvagotomy symptoms – none severe – in around 5 per cent of patients.

Keywords: Duodenal ulcer, highly selective vagotomy, outcome, recurrent ulcer, postvagotomy syndromes

Highly selective vagotomy (HSV) initially appeared to be a safe and effective treatment for duodenal ulcer. Latterly, however, the pioneering departments where the work originated have separately published studies casting doubts on its efficacy. One centre considered the long-term recurrence rate to be unacceptably high[1], while the other suggested that ulcers resistant to H_2-receptor antagonists (which today account for the majority coming to elective surgery) did badly after HSV[2].

When Amdrup and Johnstone reported their early results of highly selective vagotomy at 2–4 years follow-up[3], the ulcer recurrence rate was less than 1 per cent. With the publication of further series the recurrent ulcer rate continued to rise with the passage of time. A review of series with more than 5 year follow-up shows recurrent ulcer rates varying from 9 to 26 per cent (*Table 1*)[4–15]. The longest follow-up has come from the unit in Copenhagen which jointly introduced the procedure[1]. Not only was the recurrent ulcer rate 30 per cent at 14–18 years but of these 80 per cent were defined as 'malevolent', they either required reoperation or continuous or repeated treatment with H_2-receptor antagonists. The operations in this series were performed earlier than 1973 before the importance of denervation of the entire intra-abdominal oesophagus was appreciated[16] and when the standard length of innervated antrum was 8–10 cm. Moreover the indications for the procedure included prepyloric and pyloric ulcers for which the operation is now known to be inappropriate[17–19]. A recent study from Primrose *et al.* in Leeds[2] reported that ulcers resistant to H_2-receptor antagonists did less well surgically with a recurrence rate of 34 per cent at 5 years

The purpose of the present study is to report a series of patients who had HSV performed after 1973 for duodenal ulcer only. The objectives were first to test the risk factors claimed to be associated with failure of the operation Those studied included length of ulcer history, previous complications, preoperative acid output and its reduction after operation, cigarette smoking, and the status of the surgeon who performed the operation. Secondly we wished to establish whether recurrent

Table 1 *Recurrent ulcer rates after highly selective vagotomy – series with a minimum follow-up of 5 years*

Author	Follow-up period (years)	Total	Recurrence	%
Herrington *et al* (1986)[4]	6–13	109	10	9
Blacket and Johnston (1981)[5]	5–12	233	25	11
Liavag and Roland (1982)[6]	5–10	282	35	12
Lunde *et al* (1983)[7]	5–11	428	51	12
Kennedy (1984)[8]	5–13	242	32	13
Muhe *et al* (1982)[9]	5–6	524	73	14
Storey *et al* (1981)[10]	5–9	93	15	16
Paimela *et al* (1987)[11]	8–11	67	11	16
van Holstein *et al* (1987)[12]	10–13	100	18	18
Nilsell (1979)[13]	5–9	52	10	19
Teichmann *et al* (1985)[14]	10	68	18	26
Madsen and Kronborg (1980)[15]	5–8	100	26	26
Hoffman *et al.* (1987)[1]	14–18	106	32	30

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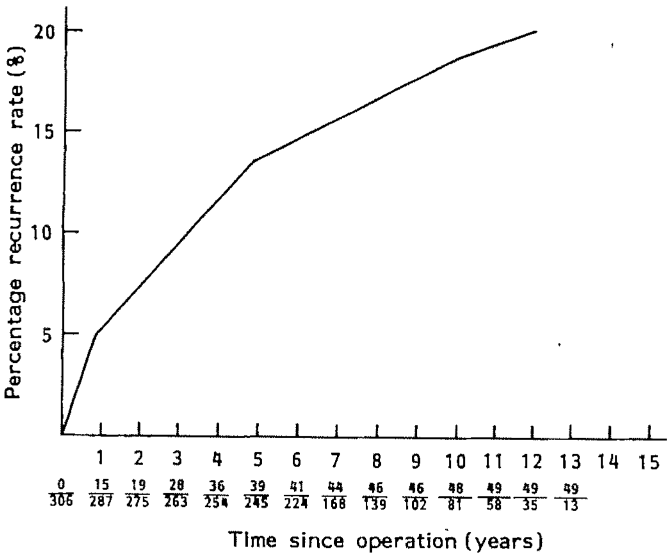

Figure 1 *Recurrent ulcer rate after highly selective vagotomy Numbers shown on the horizontal axis are the number of patients with recurrent ulceration over those eligible for analysis at each point*

ulcer after HSV was less aggressive both in terms of presenting features and ease of treatment. In other words did 'failed' HSV convert an aggressive ulcer diathesis into a milder innocuous version, with minimal symptoms, more easily treated. We also aimed to test the hypothesis that ulcers that had failed to respond to H_2-receptor antagonists did badly with HSV. Finally we sought to determine the symptoms experienced and the need for medical treatment 5–15 years after HSV.

Patients and methods

All patients undergoing surgery for peptic ulcer disease in our hospital are documented and followed up by the Gastric Follow-Up Clinic[20]. Those patients having HSV for duodenal ulcer between 1 January 1973 and 1 January 1983 were reviewed annually by postal questionnaire or at an evening clinic or by home visit A total of 307 operations were performed without operative mortality The median age was 39·6 years with a range of 12·6–70·6 years. The male to female ratio was 229:78 Seventy-six per cent (234) were cigarette smokers.

Previous ulcer complications were recorded as possible indicators of severity of the ulcer diathesis One hundred and ninety one had no previous complications, while 92 patients had previous complications, 74 had bled from the ulcer (eight with a concomitant or subsequent perforation) and 18 had a perforation alone

Pentagastrin tests were conducted using a dose of 6 μg/kg without correction for gastric loss and duodenal reflux Maximal acid output (mmol/h) was calculated as the acid output during the four 15 min periods after pentagastrin administration

Only those patients with a minimum follow-up of 5 years were considered Ten patients had died and 14 were lost to follow-up within 5 years of the operation leaving 283 (92·2 per cent) with a minimum follow-up of 5 years. In 1988 all surviving patients were reviewed by the Surgical Review Office[21] giving a 5–15 year follow-up By this time a total of 19 patients had died and 38 had been lost to follow-up leaving 250 (81·4 per cent) available Current symptoms and medical treatment were analysed in this group

The first 2 years of the study antedated the introduction of H_2-receptor antagonists and most of the 103 patients not treated by H_2-receptor antagonists came from this period Of the patients 70 had failed to heal on an H_2-receptor antagonist regimen and 101 relapsed on maintenance treatment or after cessation of treatment. No patients in the series admitted to taking aspirin and one only was on steroid therapy Three were taking non-steroidal anti-inflammatory drugs

Information from our standard questionnaire was transferred to an NCR-PC microcomputer and analysed using D Base III Plus (Ashton-Tate, Maidenhead, UK) The recurrence rate was estimated by life table methods and the significance of preoperative factors in predicting subsequent recurrence was tested by Cox proportional hazards regression

Results

Of the 283 patients available for review more than 5 years after operation, 49 (17·3 per cent) were diagnosed as having recurrent ulcer. The cumulative recurrence rate (*Figure 1*) was 13·2 per cent at 5 years rising to 19·4 per cent at 12 years. Most patients presented with epigastric pain with or without other symptoms (*Table 2*). One patient was known to have an asymptomatic recurrence revealed by routine endoscopy. It was not our policy, however, to endoscope all asymptomatic patients, so that the 'silent' recurrence rate is not known. Of the 49 recurrent ulcers, 41 were duodenal, two gastric, three prepyloric and three pyloric Thirty-nine ulcers were diagnosed at endoscopy, six at barium meal and two at laparotomy. The remaining two were diagnosed in other centres without the method of diagnosis being recorded.

Risk factors

Possible risk factors are compared in *Table 3* contrasting patients with and without recurrence There was no significant difference between the two groups in age or length of history (defined as interval between diagnosis and operation) Analysis of preoperative symptoms and their duration showed no significant difference between the groups. Patients presenting with vomiting were at higher risk at the 5 per cent level of significance. There were relatively fewer recurrences in men and relatively more in cigarette smokers but neither reached statistical significance.

A previous complication of ulcer was not associated with an increased chance of recurrence About one-third in each group had had a previous bleed and/or perforation. Nor were those ulcers resistant to H_2-receptor antagonists more likely to recur after HSV. Of the 49 patients with recurrent ulcer, 13 (26 per cent) had failed to heal on H_2-receptor antagonists, while 66 of 234 (28 per cent) without recurrence had failed to respond to H_2-receptor antagonists. (*Table 4*)

Table 2 *Presentation of recurrent ulcer in 49 patients*

Epigastric pain	36	(21 had other symptoms)
Haemorrhage	3	(1 had other symptoms)
Nausea	7	(all had other symptoms)
Vomiting	18	(16 had other symptoms)
Heartburn	7	(5 had other symptoms)
Weight loss	2	(both had other symptoms)
Anorexia	3	(all had other symptoms)
Perforation	1	
No symptoms	1	
Not known	2	

Table 3 *Recurrent ulcer – possible risk factors*

	Recurrence (n=49)	No recurrence (n=234)
Age*	37·1 (range 12·6–67·7)	40·4 (range 16·9–70·6)
Length of history*	2·1 (range 0·15–29·4)	2·1 (range 0·01–37·1)
Male†	33 (67)	180 (76·9) n.s
Cigarette smokers†	42 (86)	174 (74·4) n s.
Non-cigarette smokers†	7 (14)	60 (25·6) n.s.
Previous complications†		
none	33 (67)	158 (67·5) n s
bleed	11 (22)	55 (23·5) n s.
perforation	4 (8)	14 (6·0) n s
both	1 (2)	7 (3·0) n s.

* Median (range in parentheses); † number of patients (percentage in parentheses); n s , not significant

Table 4 *Resistance to H_2 blockers and recurrent ulcer*

	Recurrence (n=49)	No recurrence (n=234)	Total (n=283)
Failed to respond to H_2 blocker	13 (26·5)	66 (28·2)	79
Relapsed after course of H_2 blocker	18 (36·7)	83 (35·5)	101
No H_2 blocker	18 (36·7)	85 (36·3)	103

Values are numbers of patients (percentages in parentheses)

Table 5 *Percentage recurrence at 5 and 10 years according to family history*

Number of first degree relatives with diagnosis of duodenal ulcer	5 years	10 years
0	9·7 (2·3)	13·5 (3·0)
1	11·2 (3·7)	17·2 (5·0)
>1	25·9 (5·8)	33·2 (7·4)

Values are percentage (s.e.) recurrence

Table 6 *Preoperative maximal acid output studies*

	Recurrence (n=48)	No recurrence (n=225)
Preoperative maximal acid output (mmol/h)*	15–54	12–75
Preoperative maximal acid output (mmol/h)†	36·8 (10·6)	36·1 (11·3)

* Range; † mean(s.e.)

Patients with a strong family history of duodenal ulcer had a significantly higher rate of ulcer recurrence (*Table 5*).

Acid secretion studies

Maximal acid output in response to pentagastrin was recorded before operation in 273 patients and after operation in 140. The preoperative maximal acid output did not identify those at risk of recurrence (*Table 6*). Using life table analysis, postoperative maximal acid output was significantly higher ($P<0.05$) in patients who subsequently developed recurrent ulcer. The percentage reduction in maximal acid output was not, however, significantly different in the two groups. In the recurrent ulcer group, however, 10 of the 34 patients (29 per cent) showed an acid reduction of less than 20 per cent and thus could be considered to have had an inadequate vagotomy. This contrasts with only 12 out of 106 (11·3 per cent) patients without recurrence who had an incomplete vagotomy by these criteria.

Operating surgeons

Of the 19 surgeons involved in the series, five were consultants and 14 surgeons in training. The individual recurrence rate varied from 5 per cent (1 of 19) to 26 per cent (10 of 39). While the differences between the best and the worst of each group were large they were not significant and the overall consultant recurrence rate of 15·2 per cent was not significantly different from the overall recurrence rate of the surgeons in training, 19·6 per cent.

Behaviour of recurrent ulcer

Ulcer recurrence continued to present throughout the period of follow-up (*Figure 1*), the interval to recurrence varying from 1 month to 128 months after operation. The cumulative recurrent ulcer rate increased from 13·2 per cent at 5 years to 19·4 per cent at 12 years.

The treatment of the recurrent ulcers is summarized in *Figure 2*. Of the recurrent ulcers in our series, 19 could be considered innocuous, and 30 malevolent according to the classification suggested by Hoffman *et al.*[1]. Of the innocuous ulcers, five required no therapy because of minimal symptoms and three required occasional antacid or other drug treatment but not H_2-receptor antagonists. Eleven required either a single course of H_2-receptor antagonist or occasional treatment only.

The 30 malevolent ulcers included 10 which required repeated or frequent courses of treatment with H_2-receptor antagonist and 20 which required a further operation. The operations performed are shown in *Table 7*. There was no operative mortality following these revisional operations. Of the 30 malevolent recurrent ulcers, three presented with haemorrhage and one with perforation.

Current symptoms

The symptoms experienced by 250 patients 5–15 years after operation are shown in *Table 8*, comparing those with known recurrent ulcer with the others. The results are expressed as a percentage of those who had symptoms every day or most days. Overall 8·9 per cent had epigastric pain, 11·8 per cent had heartburn, 5·4 per cent dumping and 4·1 per cent diarrhoea. The commonest symptom was postcibal bloating in 21·4 per cent.

Drug treatment

Of the 240 patients who answered the question 26 (10·8 per cent) took H_2-receptor antagonists every day or most days (*Table 9*).

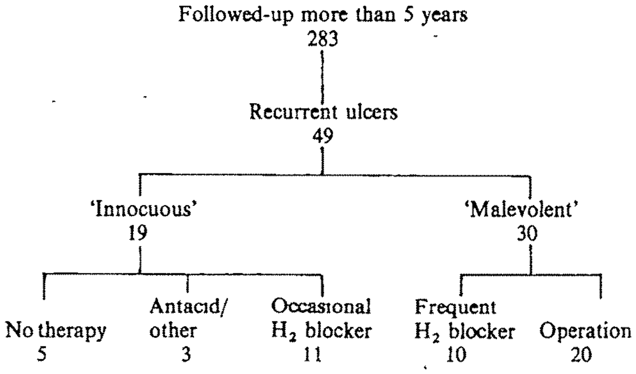

Figure 2 *Behaviour of recurrent ulcer in 49 patients*

Table 7 *Operations in patients with recurrent ulcer*

Polya gastrectomy	6
Billroth I gastrectomy	3
Truncal vagotomy and antrectomy	2
Truncal vagotomy and pyloroplasty	4
Truncal vagotomy and gastroenterostomy	1
Truncal vagotomy with pyloric dilatation	1
Gastroenterostomy	2
Simple closure of perforated duodenal ulcer	1

Table 8 *Percentage of patients 5–15 years after operation with various symptoms every day or most days* (n=250)

	All patients	Recurrence	No recurrence
Epigastric pain	8·9	22	6·3
Heartburn	11·8	23·1	9·7
Bloating	21·4	37·5	18·3
Vomiting	1·3	5·3	0·5
Dumping	5·4	15	3·5
Diarrhoea	4·1	2·4	4·4
H_2-blocker	10·7	30·8	6·9

Table 9 *Need for H_2 receptor antagonists 5–15 years after operation (eight patients did not answer this question)*

	Recurrence ($n=39$)	No recurrence ($n=203$)	All ($n=242$)
H_2-receptor antagonists every day or most days	12 (30·8)	14 (6·9)	26 (10·7)
H_2-receptor antagonists occasionally or never	27 (69·2)	189 (93·1)	216 (89·3)

Values are numbers of patients (percentages in parentheses)

Almost one-third of patients in the recurrent ulcer group took H_2-receptor antagonists on this basis and almost one-third of these took antacids in addition.

Patients assessment

Of the 239 patients who responded to the question about the success of the operation 203 (84·9 per cent) considered the operation to have been a success while 218 (91·2 per cent) considered that their symptoms were cured or improved

Discussion

The continuing rise in ulcer recurrence rate with time emphasizes the need for long-term follow-up in the assessment of highly selective vagotomy The reasons for this recurrence seem to fall into two groups. First there are those in whom a seemingly satisfactory reduction in acid output has been achieved. Only one of the possible risk factors that we studied has proved to be implicated – a strong family history of ulcer disease. This raises the possibility that the aggression of the ulcer diathesis is genetically determined but not mediated through acid output. In the second group with recurrence, acid secretion studies suggest an incomplete vagotomy. We have confirmed the large individual variation between surgeons and shown that this does not correlate with seniority or experience. Although recurrence varied greatly between individual surgeons these differences were not statistically significant. The preoperative maximal acid output is not a predictor of success or failure in either group.

Our series was performed in the era of a more complete oesophageal denervation and extension of the distal denervation of the parietal cell mass. We believe that the superiority of our results compared with Hoffman's may well be explained by these improvements in technique although our follow-up period is shorter.

In studies of more radical forms of surgery[22] we have shown that patients who 'earn' their operation by enduring symptoms for many years fare no better than those with a short preoperative history Our present study confirms that this applies also to HSV. A previous haemorrhage from or perforation of the ulcer did not predispose to recurrence after HSV. Both of these complications remain important contributors to the indications for elective duodenal ulcer surgery. It is important to know that they do not in themselves indicate an aggressive ulcer diathesis and thus do not decrease the chances of a successful HSV.

Only seven of our 49 patients with recurrent ulcer were non-smokers and two of those were considered by subsequent acid studies to have had an unsatisfactory vagotomy. Although not statistically significant this trend may mean that cigarette smoking having contributed to the failure of medical treatment can also influence surgical failure.

In this series, like those of Weaver and Temple[23] and Goodman *et al.*[24], prior resistance to H_2-receptor antagonists was not associated with increased failure of HSV, in contrast to other series[2,25]. This difference may be explained by differing definitions of failure and differences in patient compliance between the series. It is important to resolve this controversy since all patients now coming to elective surgery will have had H_2-receptor antagonists. Furthermore it is those very patients in whom these agents have failed who are selected out for surgery. This study shows clearly that a high maximal acid output, a previous ulcer complication and resistance to H_2-receptor antagonists are not associated with a poorer result.

It should be emphasized that the aim of the surgical procedure is to prevent complications and abolish symptoms. Since only four patients in our series had a bleed or perforation after HSV compared with 92 before the operation, the procedure is clearly successful in preventing these complications.

It is also successful in abolishing symptoms or reducing them to acceptable levels in about 90 per cent of patients. The commonest symptom is postcibal bloating caused by the loss of adaptive relaxation as a result of denervation of the fundus and body. We have shown that this symptom persists in the long term in some 20 per cent of patients. Our practice is to warn patients before operation of the possibility of this symptom although it is regarded as a problem by very few. The incidence of diarrhoea every day or most days was 4·1 per cent, similar to that reported in other series. Similarly only 5·4 per cent complained of symptoms of dumping and in all of these the symptoms were readily controlled by medical means Furthermore as Salamán *et al.*[26] and Muller *et al.*[27] have demonstrated these symptoms may be present in 5 per cent of subjects who have not had a vagotomy.

Approximately 10 per cent of patients overall had dyspeptic symptoms every day or most days and were required to take daily or regular antacids or H_2-receptor antagonists to control them.

This level of symptom control 5–15 years after operation indicates that the operation is successful in controlling the disease in the long term. To assess results simply in terms of recurrent ulcer can be misleading. We would support the view of Busman and Munting[28] and Byrne *et al.*[29] that measurement of symptom control is a more appropriate measure of success or failure than recurrence rate alone. We have shown that 40 per cent of recurrent ulcers are readily treated or require no treatment at all. Furthermore the side effects which resulted in the demise of gastrectomy and truncal vagotomy are less frequent and occur in a milder, less distressing form after HSV The mortality rate in the Lothian Health Board area for HSV is 0·05 per cent in over 800 procedures confirming it as the safest operation for peptic ulcer disease[30]

We judge HSV a success in providing a disease-free interval of 15 years in about 80 per cent of patients and curing or improving symptoms in some 90 per cent.

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Comparison of highly selective vagotomy with truncal vagotomy and pyloroplasty: results at 8–15 years

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In 1983 we reported the early results (mean 5 years) of a prospective randomized comparison of highly selective vagotomy (HSV) with truncal vagotomy and pyloroplasty (TVP) where all 137 operations were performed by the same surgeon. HSV was significantly better than TVP in terms of Visick grading and side-effects. The same patients were assessed at a mean of 12 years (range 8–15 years) after operation. There was no difference on assessment using Visick grading between TVP (59 patients) and HSV (57 patients) (grades I and II, 75 per cent in each case). However, 20 per cent of TVP patients (but none of the HSV patients) had undergone reoperation in the intervening period. The endoscopically proven recurrence rate was 7 per cent after TVP and 5 per cent after HSV. This long-term follow-up supports the optimism that HSV is a better operation than TVP in the elective treatment of duodenal ulcer.

Keywords: Highly selective vagotomy, truncal vagotomy, recurrent ulcer, duodenal ulcer

Truncal vagotomy and gastric drainage for chronic duodenal ulcer has a low mortality rate, but 15–30 per cent of patients develop side-effects[1–3] which are probably attributable to the loss of pyloric control. The attraction of highly selective vagotomy (HSV), introduced in 1970[4,5], depends on preservation of antral and pyloric innervation and function with avoidance of gastric drainage together with its sequelae. Uncontrolled studies on HSV[6,7] were followed by controlled trials comparing HSV with truncal vagotomy and pyloroplasty (TVP)[8], gastrojejunostomy[9] or antrectomy[10] Side-effects have been reported to be significantly fewer after HSV compared with TVP or any other drainage procedure[1–3,8–11]. Early reports on HSV showed a low frequency of recurrent ulcer of 2–5 per cent[9,12], but subsequently much higher recurrence rates of 18–30 per cent have been reported[1,13,14].

We have previously compared the results at a mean of 5 years after operation in 137 patients operated on by one surgeon and randomly allocated to either HSV or TVP[11]. HSV was a significantly better operation than TVP according both to Visick grading and to the frequency of several untoward symptoms. We have now reviewed the same group of patients at a mean of 12 years after operation.

Patients and methods

The original trial[11] included all patients under the age of 65 years who were referred to one surgeon for elective surgical treatment of duodenal ulcer between September 1972 and January 1979 Of 165 patients provisionally entered, 25 were rejected at operation for various reasons and 140 were randomly allocated to either HSV or TVP, one surgeon performed all the operations. At a mean interval of 5 years after operation, the outcome in 137 patients was assessed by two physicians unaware of which operation had been done

The long-term outcome in the same group of patients has been reassessed at a structured interview by two physicians and one surgeon who were also unaware of which operation had been done The mean interval between operation and review was 12 years (range 8–15 years). Of the 137 patients assessed at the time of the first report, 116 (85 per cent) were available for reassessment (TVP 59, HSV 57) Eight patients had died from unrelated causes (HSV five, TVP three; myocardial infarction three, carcinoma of bronchus two, road accident two, chronic alcoholism one) and 13 (10 per cent) patients could not be contacted (TVP seven, HSV six). Eighty patients (TVP 48, HSV 32) were assessed by personal interview and 36 by postal questionnaire (TVP 11 five male, six female, HSV 25. 21 male, four female) Patients were allocated a Visick grade according to the criteria modified and defined by Goligher *et al*[15] Patients in Visick grades III and IV underwent upper gastrointestinal endoscopy, unless they refused it Details of reoperations were noted and finally the patient was asked to express an opinion about the outcome of the operation. The χ^2 test was used to assess statistical significance

Results

Comparability of groups

Fifty-nine patients had undergone TVP and 57 underwent HSV. The mean follow-up time of 12 years was similar in each group. The groups were comparable for age, sex, smoking habits, alcohol intake, ingestion of ulcerogenic drugs, duration of preoperative symptoms and family history of duodenal ulcer (*Table 1*).

Overall results

The overall results are shown in *Table 2*. Using strict Visick grading, 75 per cent of each group had a good result (Visick grades I and II) and there was no significant difference between the operations in the frequency of various symptoms (*Table 3*).

Recurrent ulcer

The 29 patients (TVP 15, HSV 14) graded Visick III and IV were asked to undergo endoscopy, and 21 (TVP 9, HSV 12) consented. The endoscopy findings are shown in *Table 4*. There were no new recurrent ulcers detected in the TVP group, although four had been found at the 5-year review. Two of these patients had undergone reoperation and two were managed with H_2-receptor blocking drugs. Two previously undetected recurrent ulcers were found after HSV in addition to the one recurrence detected at the 5-year review These two patients became symptomatic at 8·5 and 9·0 years after operation. None of the three patients with recurrence after HSV has so far required a second operation.

The overall frequency of recurrence at a mean of 12 years after operation was therefore 4 of 59 (7 per cent) after TVP and 3 of 57 (5 per cent) after HSV.

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Table 1 *Comparison of treatment groups*

	TVP	HSV
Number of patients reviewed	59	57
Men	39 (66)	43 (75)
Women	20 (34)	14 (25)
Age at operation (years)*	43	42
Duration of preoperative symptoms (years)*	12	13
Smokers	23 (39)	24 (42)
Regular alcohol intake	16 (27)	14 (25)
Ulcerogenic drugs	4 (7)	5 (9)
Positive family history	13 (22)	15 (26)
Follow-up time (years)†	12·3 (8–15)	12·4 (8–15)

Figure in parentheses are percentages; * median; † mean (range in parentheses), TVP, truncal vagotomy and pyloroplasty, HSV, highly selective vagotomy

Table 2 *Overall results*

	TVP	HSV
Total no of patients	59	57
Visick grade		
I	33 (56)	35 (61)
II	11 (19)	8 (14)
III	11 (19)	12 (21)
IV	4 (7)	2 (4)
Recurrent ulcer (cumulative)	4 (7)	3 (5)
No of patients dissatisfied with operation	10 (17)	2 (4)
Reoperation	12 (20)	0

Figures in parentheses are percentages: TVP, truncal vagotomy and pyloroplasty, HSV, highly selective vagotomy

Reoperation

During the interval between the 5-year and 12-year reviews, 12 patients, all in the TVP group, had been reoperated upon pyloric reconstruction for diarrhoea and dumping had been carried out in nine patients, Pólya's gastrectomy for recurrent ulceration in two patients, and resection of an oesophageal stricture with jejunal interposition in one patient. None of the HSV patients had undergone reoperation.

Changes in Visick grading

When Visick grading at a mean of 5 and 12 years after operation was compared, 25 (42 per cent) TVP patients showed improvement; of these, 12 had been reoperated on. In the HSV group, 14 (25 per cent) patients had improved. Visick grades had deteriorated in six (10 per cent) patients after TVP and in 11 (19 per cent) patients after HSV.

Patients' opinions

Although Visick grading showed no significant difference between the two groups, 10 (17 per cent) patients in the TVP group expressed dissatisfaction with the result of the operation compared with two (4 per cent) patients in the HSV group The symptoms which were associated with dissatisfaction after TVP were epigastric fullness and nausea (seven patients) and heartburn and epigastric discomfort (three patients). Both patients expressing dissatisfaction after HSV complained of epigastric fullness and heartburn

Discussion

There is no doubt that HSV is a conceptually attractive operation. However, a high incidence of recurrence in many reports is a serious drawback A recent 14–18-year follow-up[14] is particularly interesting: the symptomatic recurrence rate was 30 per cent (an additional 9 per cent may have had recurrence); a good result (Visick grades I and II) was obtained in 57 per cent, but 42 per cent were graded Visick IV In contrast, our results in terms of recurrence (5 per cent) and Visick grading at a mean of 12 years are favourable, although not quite so good as at 5 years. One characteristic of the Aberdeen series is that all the operations were performed by the same surgeon Although Hoffmann and associates[14] saw no difference in the frequency of recurrent ulceration among various surgeons, many others have emphasized surgeon-related variability in the outcome of HSV[7,16–19].

After HSV, the three symptomatic recurrent ulcers (all duodenal) were detected within 9 years and all were well controlled with H_2-receptor antagonist therapy. In contrast, of the four patients with recurrent ulcer after TVP, two were reoperated on. It is acknowledged that asymptomatic patients were not examined endoscopically and that two patients graded Visick III or IV (because of symptoms of epigastric fullness and flatulence) after HSV refused endoscopy.

Visick grading is not an entirely satisfactory method of assessment of the functional result of peptic ulcer surgery. Its subjectivity and liability to observer variation in interpretation is an inherent drawback and, in particular, the differentiation between Visick grades II and III may not be clear-cut. Although patients in Visick grade III are regarded as having an unsatisfactory outcome, they themselves may express a favourable opinion, which may be a true reflection of their satisfaction After TVP, ten (17 per cent) patients were dissatisfied with the outcome, whereas only two (4 per cent) were dissatisfied after HSV

Comparison of the 5- and 12-year results shows interesting changes. At 5 years, on Visick grading, HSV (Visick grades I and II, 87 per cent) was a significantly better operation than TVP (Visick grades I and II, 70 per cent). The 12-year review, however, shows no difference in Visick grading. With the passage of time, Visick grades have improved in the TVP group and have become less good in the HSV group, although none of these changes is statistically significant The important reason for improvement after TVP was the influence of reoperation. Of the 21 patients who were previously Visick grades III and IV at 5 years after TVP, 12 had undergone a second operation in the intervening period which resulted in conversion to Visick grades I and II in all 12 patients.

Table 3 *Symptoms elicited at review*

	TVP ($n=59$)	HSV ($n=57$)	*P*
Epigastric fullness	13 (22)	10 (18)	n.s.
Flatulence	5 (8)	8 (14)	n s
Diarrhoea	7 (12)	2 (4)	n s.
Nausea	10 (17)	5 (9)	n.s.
Heartburn	12 (20)	14 (25)	n.s.
Pain	12 (20)	4 (7)	n s
Vomiting	8 (14)	6 (11)	n s
Dumping	5 (8)	3 (5)	n s

Figures in parentheses are percentages; TVP, truncal vagotomy and pyloroplasty; HSV, highly selective vagotomy; n.s., Not significant

Table 4 *Endoscopy findings in Visick grades III and IV*

	TVP	HSV
No. of endoscopies requested	15	14
No of endoscopies performed	9	12
Normal	2	7
Hiatus hernia	2	1
Gastro-oesophageal reflux	4	0
Gastritis	3	0
Gastric stasis	3	0
Recurrent ulcer	0	2

TVP, truncal vagotomy and pyloroplasty; HSV, highly selective vagotomy

Pyloric reconstruction was the most common second operation and the high frequency of nine such operations in a total of 70 patients having had TVP in this trial requires explanation. It may or may not be relevant that a long (6–7 cm) pylorotomy was routinely made (with a modified Finney reconstruction), although we are uncertain whether the length of the pylorotomy is a material factor in the frequency of symptomatic over-rapid gastric emptying. We believe that the reasons for the relatively large number of reconstructions are, firstly, that these patients had been carefully and critically reviewed so that symptoms which might not have resulted in re-referral were disclosed; secondly, our favourable experience with the relative simplicity and good results of pyloric reconstruction[20] inclines us to offer the procedure to symptomatic patients when others might be more conservative.

Although HSV is a technically more demanding procedure, it is, in our hands, a clearly superior operation to TVP, and long-term follow-up supports this optimism.

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Simple closure of perforated duodenal ulcer: a prospective evaluation of a conservative management policy

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One hundred and thirteen consecutive patients admitted with a perforated duodenal ulcer over a 5-year period (1978–82) and treated by simple closure have been followed prospectively over a median period of 43 months. Patients were divided into two categories according to their previous history of dyspepsia; group 1 (66 patients) with a chronic history of more than 3 months and group 2 (47 patients) where there was no history of dyspepsia or a history of less than 3 months duration. The follow-up periods were similar (group 1, 44 months; group 2, 43 months). The overall recurrence rate was 42 per cent and to date only 14 per cent of the total group of 113 patients have required a definitive operation. The incidence of ulcer recurrence was higher in group 1 than in group 2 in terms of total recurrence (group 1, 50 per cent; group 2, 32 per cent) and patients requiring further surgery (group 1, n = *14, 21 per cent; group 2,* n = *7, 15 per cent). Five of these 21 patients required an emergency procedure for haemorrhage or reperforation (group 1,* n = *2; group 2,* n = *3). There were no significant differences between the 5-year predictive recurrence rate or the requirement for definitive surgery between the groups. Five of the 27 patients currently on medical treatment have required maintenance treatment while the remaining patients receive active treatment for a mean of 20 per cent of the time since they developed recurrent ulceration. These results support continuation of our 'wait and see' policy following simple closure of perforated duodenal ulcer, even in patients with a history of chronic dyspepsia.*

Keywords: Perforated duodenal ulcer, simple closure

Despite the swing towards conservatism in the management of patients with uncomplicated duodenal ulcer disease, many centres today still follow the traditional aggressive surgical policy in patients with perforated duodenal ulcer[1–8]. Definitive surgery is carried out either at the time of perforation[6] or after simple closure[7,8] on patients with a history of chronic dyspepsia (more than 3 months duration) and in young patients with acute ulcers Justification for this approach is based largely on reports of a high incidence of recurrent ulceration[8–11] and complications[5,9,12] in such patients after simple closure.

In a previous study from our institution, the histological findings in specimens taken from the edge of the ulcer at the time of simple closure were similar in patients with acute and chronic ulcers[7]. A number of other studies have also questioned the difference between the natural history of so-called acute and chronic ulcers[3,11–13]. Against this background we designed this prospective study to investigate the validity of our previous treatment strategy where the indication for subsequent definitive surgery was based mainly on a previous history of dyspepsia. We also wanted to assess whether our impression that a 'wait and see' policy after simple closure was a reasonable alternative in our patient population.

Patients and methods

One hundred and thirteen patients admitted to Groote Schuur Hospital over a 5-year-period (1978–82) with a perforated duodenal ulcer treated by simple closure have been documented and followed-up prospectively at our Gastric Follow-up Clinic After discharge from the hospital, patients were given antacids to take when required and were seen between 6 and 12 weeks for the first follow-up. A detailed clinical history was obtained regarding a past history of dyspepsia and patients were divided into two groups. group 1 (chronic ulcer) when there was a history of dyspepsia of more than 3 months and group 2 (acute ulcer) when the history was of shorter duration. Further follow-up was at annual intervals but more frequently whenever recurrent symptoms developed Routine endoscopy was performed on the first visit and where possible on subsequent visits, regardless of symptoms. Patients who developed symptomatic or asymptomatic recurrent ulceration were treated with full dose H_2-receptor antagonists and then re-endoscoped after 6 weeks to ensure healing As a rule treatment was stopped once healing was achieved. More prolonged treatment or maintenance treatment were considered in patients with troublesome or frequent recurrences or in elderly high risk patients Indications for definitive surgery were similar to those used for uncomplicated duodenal ulcers. Surgery was considered only after two failures of adequate medical treatment or in the event of troublesome recurrences while on maintenance therapy The end points studied were ulcer recurrence requiring medical or definitive surgical treatment and emergency surgery for complications (bleeding and reperforation).

Statistical analysis

The Fisher's exact test was used to compare ulcer recurrence rates and the Breslow generalized Wilcoxon test for recurrence free rates.

Results

Sixty-six patients were categorized as chronic ulcers (group 1) with a mean (s.d.) age of 38 (12·7) years; 49 of the 66 (78 per cent) were males. The mean (s.d) age of the 47 patients with acute

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ulcers (group 2) was 43 (18 37) years and 37 (78 per cent) of them were males. The median periods of follow-up were similar in the two groups; group 1 = 44 months (range 6 to 88 months) and group 2 = 43 months (range 10 to 96 months) *Table 1* shows the incidence of ulcer recurrence in the two groups and their subsequent management by medical treatment alone, definitive surgery after failure of medical treatment and emergency surgery for further complications.

Five patients in the acute group and six in the chronic group had asymptomatic duodenal ulcers detected on routine endoscopy. These were treated medically with full dose H_2-receptor antagonists. There were two prepyloric ulcers and one gastric ulcer amongst the patients who developed a recurrence during the follow-up period and were treated similarly.

Of the patients on medical treatment, only five have required prolonged maintenance treatment (two because of age and three by their own choice). The remaining patients received active medical treatment for 20 per cent of the time (129 of the 658 months) of observation. The three complications in the acute group were due to reperforation while in the chronic group there was one bleed and one perforation

Recurrence rates were higher (not statistically significantly so) in group 1 than group 2 in terms of total recurrence and patients requiring a further definitive operation. The total 5-year cumulative recurrence rates (*Figure 1*) and the number of patients who required a definitive operation remained similar (*Figure 2*). The cumulative percentage of recurrence-free rates were similar when patients over and under the age of 30 were compared. In this series there were only 14 patients over the age of 60 years of whom 11 had acute ulcers. Five of these 14 had a recurrence (median follow-up 32 months), compared with 44 of the 99 under the age of 60 years (median follow-up 43 months) and 16 of the 34 younger than 30 years (median follow-up 47 months). These differences, however, were not statistically significant. The recurrent ulcers were uncomplicated in all patients over the age of 60 years.

Table 1 *Management of ulcer recurrence after simple closure*

	Further medical treatment	Elective surgery	Further emergency surgery	Total
Group 1 (chronic) *n* = 66	19	12	2	33 (50)
Group 2 (acute) *n* = 47	8	4	3	15 (32)
Total *n* = 113	27	16	5	48
	(23·9)	(14·2)	(4·4)	(42·5)

Values in parentheses are percentages

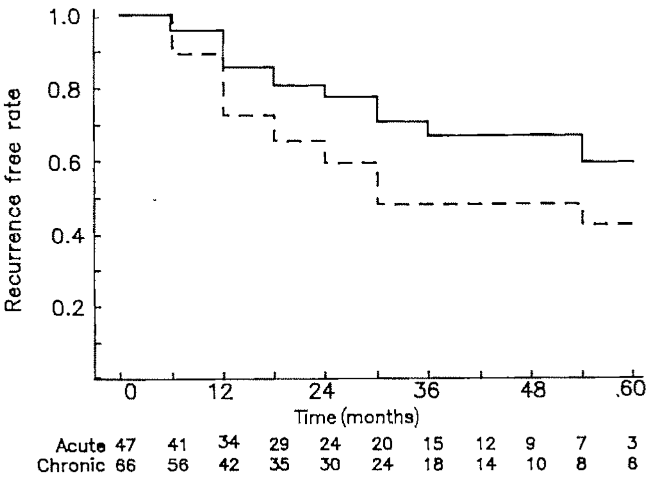

Figure 1 *Cumulative percentage free recurrence rate to first recurrence (treated medically and ulcer related complications). Group 1 (chronic dyspepsia patients,– – –) and group 2 (acute dyspepsia patients,——). Figures at the foot indicate number of patients followed during the follow-up period.* P=0·0523 (*Wilcoxon test*)

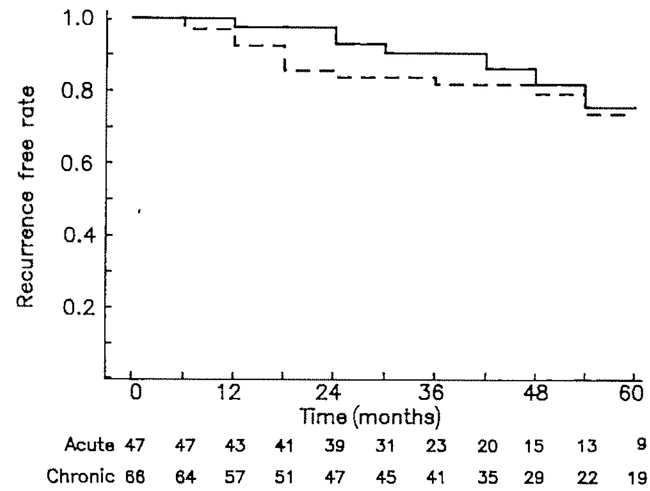

Figure 2 *Cumulative percentage free recurrence rate (definitive surgery). Group 1 (chronic dyspepsia patients,– – –) and group 2 (acute dyspepsia patients,——) Figures at the foot indicate number of patients followed during the follow-up period*

Seven of the 113 patients were on non-steroidal anti-inflammatory drugs, five of whom were over the age of 60 years. Three of these patients died of unrelated causes. One patient was free of ulcer recurrence after 60 months; two required a further definitive operation and another remained well on maintenance treatment.

Seven unrelated deaths (all in the acute group) occurred during the follow-up period. The causes of death were; myocardial infarction, 2; cardiorespiratory, 2; ruptured abdominal aneurysm, 1; carcinoma of the oesophagus, 1; and motor vehicle accident, 1

Discussion

Before commencing this study, our unit treated all perforated duodenal ulcers by simple suture closure followed by definitive surgery 6 weeks later in both the chronic group and in the subset of younger patients in the acute group[7]. The results of the present study questions the validity of this policy and the traditional arbitrary division between so-called acute and chronic ulcers. Although patients in the chronic group had an appreciably higher incidence of ulcer recurrence than those with acute ulcers, the incidence of 50 per cent after a median follow-up period of 43 months cannot justify routine referral for definitive surgery We could not confirm the increased risk of ulcer recurrence in patients under the age of 30 years[11] and the notion that elderly patients would be at greater risk was not confirmed in this study. Indeed, they seemed to have fared better than their younger counterparts.

Most patients with ulcer recurrences were well-controlled on intermittent medical treatment and to date only 14 per cent have required a definitive operation It is of interest that the natural history after simple closure of duodenal ulcer perforation appears to follow a more benign course than that encountered in patients with uncomplicated ulcer entered into drug trials at our institution[14] and elsewhere[15]. The recurrence rates in these latter reports were of the order of 70–80 per cent at 1 year. While such a comparison may not be entirely legitimate, it does support the view that treatment policies in patients after simple closure of perforated duodenal ulcers do not necessarily have to be different from those with uncomplicated ulcers.

The low incidence of subsequent complications without any related deaths supports a conservative approach after simple closure and would oppose the recent trend of carrying out a highly selective vagotomy at the time of the perforation. Although highly selective vagotomy has been shown to be safe in the management of perforated duodenal ulcers[6,16–22] and as effective as in the elective situation[23], patient selection for a prolonged emergency operation and the availability of an experienced surgeon 24 h a day are further deterrents to such an approach.

We conclude that simple closure followed by an expectant policy remains the treatment of choice in the majority of patients who present with a perforated duodenal ulcer. The operation is a simple and safe procedure even in the hands of an inexperienced surgeon. An expectant policy and treatment of ulcer recurrences with current medical therapy[24] have proven to be both safe and effective. This study highlights possible epidemiological differences in the behaviour of peptic ulcer disease and would caution against formulating treatment polices based on published data from different geographical areas.

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Intragastric balloons for morbid obesity: results, patient tolerance and balloon life span

Sixty morbidly obese patients were treated with 88 intragastric balloons. An air-filled intragastric balloon was used, which was permanently connected to an inflation catheter exiting through the nose. Patients were evaluated for loss of body weight and tolerance of the balloon; the balloon was inspected for efficacy and safety. A mean total loss of body weight of 21 kg was obtained after a mean of 39 weeks in 15 men (mean age 37·7 years) and 45 women (mean age 36·2 years), with a mean initial weight of 127·9 kg. The maximum rate of weight loss occurred in the first 6 months, with a steady decrease of 1 kg per week; thereafter the rate declined. Subjective complaints were infrequent and consisted of nasal discomfort or abdominal symptoms. Intolerance in 12 per cent of patients was due to enhanced hunger (one patient), nasal pulling sensation (four patients) and symptomatic ulcer (two patients). Fifteen patients asked for removal of the well functioning balloon after a mean of 169 days; 14 of the 15 balloons were still airtight. Forty balloons failed prematurely. Nine were retrieved orally and 31 were passed per anum, *of which 28 passed with mild abdominal cramping, two patients required transabdominal puncture and one needed laparotomy. Even the 40 prematurely removed balloons remained* in situ *for a mean of 108 days; only one-third showed leakage. As yet, 33 well functioning balloons have been* in situ *for a mean of 167 days. Well functioning balloons deflated at a rate of 2·3 ml per day. Malfunctioning of the balloon was due to leakage in 12 cases and to clogging of the inflation catheter in three cases. Major complications (8 per cent) included two gastric ulcers and three cases of mild ileus. One ileus patient required surgery (2 per cent). The reported intragastric balloon model is effective and safe. We recommended this type of balloon as a weight reducing adjuvant therapy before bariatric surgery.*

Keywords: Intragastric balloon, morbid obesity, weight reduction programme

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Despite short-term responses to dietary programmes, drug treatment, behavioural therapy and schedules of physical training, obesity is often called an incurable disorder. Long-term results of various multidisciplinary approaches have been disappointing, often with a step-wise increase in body weight to the original weight or more[1–3]. Morbid obesity is an even more complex disorder owing to the obligatory massive weight loss and increasing problems of maintaining any reduction. Ultimately, bypass operations or gastroplasty are considered, but this may not be feasible because of the high risks. Therefore, new approaches to management are needed.

Intragastric balloons were proposed as a promising, non-invasive procedure, not only for weight reduction but also for preparing the patients for operation. However, the main problem with balloons is their life span and the sequelae on desufflation[4–11]. Moreover, little information has been given about the weight loss and it is usually without details of long-term follow-up and the balloon-free period.

Therefore, we instituted a weight reduction programme of intragastric balloon positioning combined with a very low calorie diet of normal food in a multidisciplinary setting. The purpose was to evaluate prospectively the efficacy, tolerance and safety of intragastric balloons and to analyse the weight profile in the balloon-free period.

Patients and methods

Patients

Patients were eligible if they had a Quetelet Index (Body Mass Index, kg/m^2) of more than 40 or a Quetelet Index of more than 30 combined with severe systemic complications from obesity, such as pulmonary disease (requiring ventilatory support), the Pickwickian syndrome, haemorrhagic stroke, hypertension, hyperlipidaemia or diabetes[12]. Exclusions were related to the diet (severe hepatic or renal disease, pregnancy) or to the balloon (large hiatal hernia, active peptic ulcer disease, mental deficiency). All patients gave informed consent to the study protocol.

After a screening physical examination, blood tests for haematology and chemistry (electrolytes, uric acid, glucose, creatinine, erythrocyte sedimentation rate, haemoglobin, haematocrite, PTT, platelet and white blood cell counts, urea nitrogen and liver enzymes) were carried out. Endocrine disorders had been excluded. Further screening included ECG and upper gastrointestinal endoscopy. Those with incompetence of the lower oesophageal sphincter or with evidence of gastro-oesophageal reflux had oesophageal manometry and were monitored for oesophageal pH for 24 h.

A total of 60 morbidly obese patients were accepted for the study between February 1984 and February 1986: 15 men with a mean age of 37·7 years (median 37, range 17–62 years) and 45 women with a mean age of 36·2 years (median 33, range 18–70 years). They entered the metabolic ward and were submitted to a strict dietary regimen and regular check-up. A diet of 1680–2100 kJ (400–500 kcal) for women and

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of 2100–2940 kJ (500–700 kcal) for men was prescribed. A minimum intake of 30–40 g of high biological value protein and 30–50 g of carbohydrates was stressed, as was the intake of ample fluids (more than 2·5 litres). Supplementary multivitamins included all vitamins (except for vitamin K) and also calcium, iron, copper and zinc Whenever indicated, potassium and magnesium supplementation was given

Regular follow-up consisted of daily weight, fluid balance, pulse rate and blood pressure Blood haematology and chemistry were monitored twice a week. The urinary excretion of electrolytes and uric acid, creatinine, urea nitrogen and total nitrogen were measured Breakdown of body proteins and of fatty tissues were evaluated by extensive laboratory investigations of blood and urine

On the second day of admission, the intragastric balloon was positioned, and dietary treatment, physical training and psychological intake was started Common abnormalities were ketosis, hyperuricaemia and hypoglycaemia, but they required no specific treatment Orthostatic hypotension occasionally warranted hospitalization

After discharge from hospital, the patients were examined weekly during the first 3–6 months and twice per month thereafter. Electrolytes, liver enzymes, renal function, glucose and uric acid were monitored twice a month The laboratory investigation of protein and fat breakdown, gastrin values and ECG were repeated monthly.

At each visit subjective complaints were recorded and dietary consultation was obligatory. Behavioural treatment (once per month) and physical training were optional. Behavioural therapy included techniques of stimulus control, self-monitoring, slowing of eating and writing shopping lists[13] Physical exercise consisted of 1 hour of fitness training and 1 hour of swimming per week.

Methods

The pear-shaped intragastric balloon consists of a single walled balloon of polyurethane elastomer (wall thickness of 0·12 mm) connected by a valve flap to a 1·30 m inflation catheter of natural polyurethane elastomer with an outer diameter of 1 mm (*Figure 1*) The balloon is sealed along the circumference. Before insertion, airtightness was tested by immersion under water The folded balloon was swallowed by the patient and the inflation catheter was rerouted from the mouth to the nose. The balloon was inflated with 300 ml of air and the tube was locked with a stopper and taped at the nostril Subsequent fluoroscopy confirmed the correct position of the balloon· in the supine position in the antrum and in the fundus when upright Two improvements to prevent leakage were attempted but discarded First, 2 ml of petroleum jelly was instilled in 10 balloons This was problematical because it obstructed the valve flap and contributed to complications Secondly, 15 double layer balloons were used but this model was more difficult to swallow and actually leaked more frequently.

Whenever abdominal cramping or a feeling of hunger were mentioned during the course of treatment, desufflation and appropriate re-insufflation were carried out After some time, the patients were instructed to re-insufflate the balloons themselves Balloons were inflated with 300 ml of air which was usually well tolerated However, in 19 instances desufflation to 250 ml was necessary, twice after a severe vasovagal collapse. At follow-up, on 45 occasions, adjustment of the volume of air was necessary because of abdominal cramping or hunger feelings Unexpected balloon expansion was seen on three occasions. once while flying, once due to abnormal environmental circumstances (42°C) and once in a patient with nocturnal oxygen supply

Removal of the balloon at the request of the patient (elective removal) was simply carried out by desufflation and by gently pulling on the tube. Gradually deflating balloons left the stomach and passed into the small intestine. After desufflation some could be retrieved orally but most could not be retrieved and were allowed to pass *per anum* If necessary, 10 ml of water soluble contrast medium was injected into the balloon to enable its route to be visualized Endoscopy was performed to assess possible mucosal injury after each balloon removal or reinsertion. All recovered balloons were tested for airtightness

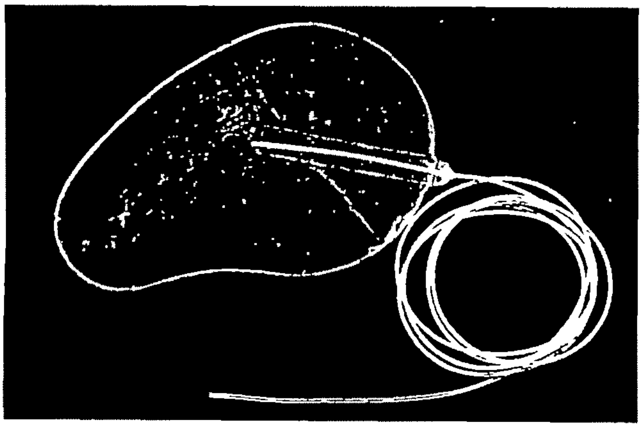

Figure 1 *The intragastric balloon with the inflation tube and the valve flap*

Evaluation of the results

The results were analysed for the whole group and separately for the time of balloon treatment as well as for the balloon-free period The patients were divided into three groups· group I ($n = 15$) had the balloon voluntarily removed, group II ($n = 13$) had prematurely and accidentally lost the balloon, and group III ($n = 33$), including one patient initially admitted to group I, were under treatment with well functioning balloons

Results

Weight reduction

At the start, the mean Quetelet Index of the 60 patients was 43·5 (median 42·5, range 35–69) and the mean percentage of weight above Ideal Body Weight (Metropolitan Life Insurance Company Tables 1983, midpoint of medium frame) was 196·6 per cent (median 194·9, range 156·9–308·3). The average weight for the whole group was 127·9 kg; 142·9 kg for males and 122·8 kg for females.

By the end of the study, a mean (standard deviation) weight loss of 21 (14·2) kg was obtained for the whole group after a mean (s.d.) total follow-up of 39·2 (21·8) weeks The Quetelet Index decreased from 43·5 (5·9) to 36·7 (6·1) and the percentage of weight above ideal weight fell from 196·6 (27·1) to 164·2 (26·5) for the whole group. The gradual reduction in body weight and the fluctuations at follow-up are depicted in *Figure 2*. Men obtained a mean maximum weight loss of 29·4 kg in a mean of 30·5 weeks, which signified a decrease in overweight from 196 to 153 per cent. For women the figures were 22·5 kg and 23·7 weeks, with a decrease in overweight from 199 to 163 per cent. Both men and women showed a levelling-off at long-term follow-up

Group I. In the balloon period (29·2 (14·1) weeks) these 15 patients needed an average of 1·4 (1–2) balloons. They lost 22·9 (11·6) kg (*Table 1*). Follow-up (up to 61·8 (22) weeks) showed a final overall weight loss of 22·2 (10·3) kg Thus in the balloon-free period only a slight gain in weight was noted Nine patients showed weight loss on removal of the balloon and either continued to do so or had a stable weight thereafter. Six patients, with an initial huge loss of weight, gained in weight before and after removal of the balloon. This reversal while on balloon treatment occurred after 22·5 weeks

Group II These 13 patients had an average of 1·4 balloons (1–3) during 29·7 (13·7) weeks of treatment. They lost 21·4 (10) kg and thereafter they regained some weight (*Table 1*) By the end of the study after 40 (16) weeks, this resulted in an overall decrease of 20·5 (11·9) kg. Again, patients who had lost weight with a balloon either continued doing so or stabilized Five patients already gaining weight by the end of the balloon period pursued this course without a balloon. The switch from weight loss to weight gain was seen after 28·5 weeks of balloon treatment.

Group III. These 33 patients needed 1·5 balloons (1–4) for a decrease of 21·3 (15·4) kg in 30·4 (17·4) weeks (*Table 1*). Thirteen are still losing weight, whereas 20 showed a gain of 3·2 (2·5) kg, despite the balloon. The change from weight loss to gain was observed after 23·5 weeks.

Tolerance of the balloon

Over 1000 outpatient consultations were recorded for these 60 patients Complaints were divided into problems caused by the nasal tube and mechanical symptoms related to the stomach (*Table 2*). A pulling sensation at the nose and up and down

Table 1 *Weight loss for the period of balloon treatment and for the total follow-up period up to the completion of the study. Data are given for the main groups and according to the patterns of weight change observed before balloon removal*

	Balloon treatment		Total follow-up	
Groups and pattern of weight change	Weight loss (kg)	Time (weeks)	Weight loss (kg)	Time (weeks)
Group I				
Electively removed ($n=15$)	22·9 (11·6)	29·2 (14·1)	22·2 (10·3)	61·8 (22·0)
Weight loss ($n=9$)	22·8 (8·7)	24·9 (12·5)	24·0 (7·5)	61·7 (15·1)
Weight gain ($n=6$)	23·1 (15·1)	35·7 (13·9)	20·8 (12·3)	62·0 (27·2)
Group II				
Prematurely removed ($n=13$)	21·4 (10·0)	29·7 (13·7)	20·5 (11·9)	40·0 (16·0)
Weight loss ($n=8$)	25·0 (9·9)	20·1 (7·1)	25·3 (12·8)	33·1 (12·4)
Weight gain ($n=5$)	15·6 (6·8)	45·0 (5·2)	12·0 (8·8)	54·2 (13·3)
Group II				
Still functioning ($n=33$)	21·3 (15·4)	30·4 (17·4)		
Weight loss ($n=13$)	28·9 (20·8)	23·5 (14·3)		
Weight gain ($n=20$)	16·3 (7·2)	35·0 (17·8)		

Numbers in parentheses indicate s.d

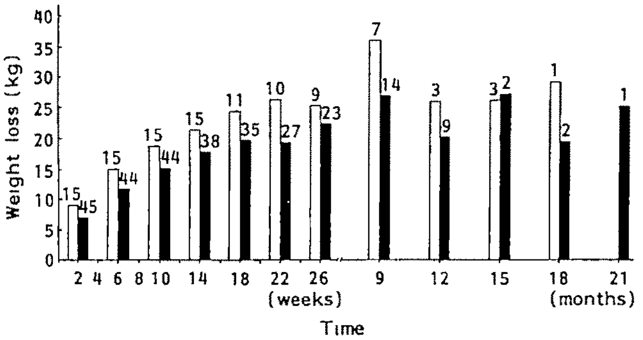

Figure 2 *Long-term changes in body weight for men and women.* ☐, *men,* ■, *women, numbers at the head of columns show numbers of patients*

Table 2 *Balloon tolerance in 60 patients at 1027 consultations*

	No of patients	No. of complaints
Tube connected at the nose		
Pulling sensation at the nose	42	106
Up and down movement	12	13
Slipping away of the tube	30	30
Mechanical symptoms of the stomach		
Nausea	28	52
Vomiting	11	13
Heartburn	27	60
Pain	34	82
Belching	30	57

movement of the tube was felt upon fast ingestion of large amounts of food and confronted the patient with incorrect eating behaviour. Thirty times the tube slipped away but could be caught orally in 20 or retrieved by gastroscopy in five patients. Five times the balloon with the tubing left the stomach and passed with the stools.

Gastric symptoms included pain, nausea, heartburn and vomiting Fifteen patients experienced discomfort during episodes of binge eating and self-induced vomiting. Abdominal cramping due to involuntary balloon expansion was seen in three patients. Readjustment of balloon volume was required 64 times. Two patients had a symptomatic gastric ulcer at endoscopy after 3 and after 19 weeks. Another four patients with a history of peptic ulcer tolerated the balloon well without ulceration Frequent control endoscopy showed only one asymptomatic ulcer in the 22nd week of intragastric balloon therapy.

Life span of the balloon

In group I, 15 balloons were removed on request because of achieving the desired weight loss (7), intolerance (4) and symptomatic ulceration (2). One patient ascribed enhanced hunger feelings to the balloon and in another patient the balloon could not be desufflated because of a clogged tube. This balloon had to be punctured by endoscopy The 15 removed intact balloons remained in place for a mean of 168·8 days (range 21–365 days).

Forty gradually deflating balloons were present in the 13 patients of group II who finally decided to continue their diet without further balloon positioning. Oral retrieval was possible in eight One had to be punctured by endoscopy because of knot formation in the tube Anal passage occurred 31 times after a period of mild abdominal cramping in 28 cases, which cleared immediately after the balloon had been desufflated by the nasal tethered tube. One patient underwent surgery for suspected intussusception which was not found. The surgeon moved the balloon from the small intestine into the colon Twice the tube was clogged. These balloons could not be desufflated and had to be punctured through the abdominal wall under sonographic guidance with subsequent successful desufflation and anal passage. The mean life span of the balloon was 108·1 days (range 5–340 days). Thirty-three balloons are still functioning and have been in place for a mean of 166·8 days (range 23–455 days).

It was surprising that even desufflation of 25 ml was felt by the patient as a recurrent feeling of hunger. After more experience was gained, the patients were allowed to correct any suspected leakage, but had to report on the frequency and amount of leakage. Leakage was noted 354 times in 12 527 balloon days. A total amount of 28 950 ml of air was lost, thus the average balloon lost 2·3 ml per day.

Balloon leakage, visible by immersion under water, was present in only 12 of the 46 evaluable balloons. Clogging of the tube (three times) and knot formation (once) interfered with the safety of air control.

Discussion

Intragastric balloon treatment was proposed as a promising, non-invasive procedure in morbid obesity. In early reports, some authors studied balloon survival, others the weight loss, and occasionally both items have been discussed, but not in relationship to one another[4–11]. Data on long-term follow-up and on the weight changes in the balloon-free period are lacking. Even the results presented at the 5th International Congress on Obesity[14–17] cannot be compared because of differences in balloon design, methodology of the study, etc.

For this reason, we first analysed the whole group as one entity, which allowed comparison with data from the literature. Our results, with weight loss at a rate of 1 kg per week in the first half year, compare favourably with other aggressive measures such as modified fasting[18] or surgery[19]. The levelling-off thereafter is a well known phenomenon. In this plateau phase the benefit of our treatment, while not outstanding, is equal or superior to other available techniques. Two single blind trials and two double blind crossover studies have evaluated sham *versus* Garren–Edwards balloon treatment[20]. These studies reported a weight loss of only 0·6–0·95 kg per week in the first 3–4 months whereas a better and more sustained reduction of 1 kg per week in the first half year was found in this study. Garren *et al.* reported a weight loss of 19 kg over a 6-month period in 144 morbidly obese patients, treated with the tubeless Garren–Edwards balloon[17].

Since obese patients notoriously regain weight after aggressive slimming programmes, the long-term results and the weight profile, both in the on-treatment and the off-treatment group, were studied. Despite the limited number of patients the off-treatment group was divided into patients who voluntarily asked for removal (group I) and into patients who had prematurely lost their balloons (group II). Group III is still being treated Forty per cent of patients in group I and 38 per cent in group II regained some weight towards the end of the balloon treatment episode. It remains to be seen whether this reflects some boredom in the first group, after a long treatment period on a very low calorie diet, or an early and true sign of impending balloon failure in the second group. However, the finding that the reversal of weight loss into weight gain occurred at 23 and 29 weeks in groups I and II might also reflect the maximal balloon benefit. Moreover, the pattern of weight loss appears to be a good predictor for the final outcome and may be of value in decision making. For instance, a patient gaining weight with a functioning intragastric balloon should have the balloon removed or not replaced if dysfunctioning because further benefit is unlikely. Further studies have to investigate whether those patients are less suitable candidates for gastroplasty.

The most promising data concerned the life span of the balloons. On average, 1·5 balloons were necessary per patient. Functioning balloons, removed on request or still *in situ*, remained for 24 weeks. Leakage occurred after 15 weeks, with a visible crack and leak in only 26 per cent. In the remainder, the gradual deflation of 2·3 ml per day was not properly replaced. A German study showed 31 out of 108 patients with a well functioning balloon for a mean of 4·5 months[8]. In Garren's study 9 per cent of the balloons survived less than 3 months[17]. Neither of the two papers discuss the reason for balloon failure.

The balloon appears to be well tolerated, as only four patients (7 per cent) had severe complaints of nasal discomfort and two patients (3 per cent) developed symptomatic ulcers. We presume that the shape and the insignificant weight of this balloon model explain the low incidence of gastric mucosal damage. With other types of balloons, gastric ulcers were seen in from 1 per cent up to 20 per cent of patients[20]. We did not observe the high rate of intolerance (25 per cent) reported by others[21]. This was probably because of the higher (600 ml) content and the inability to readjust its content.

We do not know to what extent the weight reduction was caused by other factors such as the frequent visits to the clinic and the advice of the dietitian. Compliance to the behavioural treatment sessions was poor, in contrast to a good attendance at physical training.

The promising results of this prospective study may give the intragastric balloon a place among other therapeutic modalities. It is a simple, fully reversible method with a low and acceptable risk of complications. However, the long-term efficacy has still to be demonstrated and further comparison between this non-surgical method and surgical intervention is needed, as well as double blind controlled studies of sham and balloon treatment. However, with our design this is impossible as the patients controlled and inflated the balloon themselves. We reserve this method for morbid obesity only. Where bariatric surgery is preferred, weight loss facilitated by balloon positioning before operation might make patients more suitable for planned surgery. Balloon treatment itself may be of help as a preoperative screening procedure.

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Vertical Silastic ring gastroplasty: a 6-year experience

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Vertical Silastic® ring gastroplasty was carried out in 71 patients as treatment for morbid obesity. The mean excess weight loss at 6 months (59 patients) and 2 years (43 patients) was 48 per cent and 65 per cent respectively. Subsequently the weight stabilized around this level with 58 per cent of the excess weight lost at 5 years (14 patients) postgastroplasty. Five patients (7 per cent) failed to lose weight. Sixteen patients (23 per cent) required revision for technical complications but continued to lose weight or to maintain a satisfactory weight. Vertical Silastic ring gastroplasty is an effective surgical method of achieving sustained weight loss.

Keywords: Morbid obesity, gastroplasty, weight loss

Since the introduction of gastric partitioning or gastroplasty by Mason[1] and Gomez[2], the procedure has undergone numerous modifications[3–6]. Horizontal gastroplasty[7] and gastric banding[8], the separation of the stomach into two compartments by stapling or a band passed across the upper part of the stomach, are effective methods of reducing weight but carry a high complication and reoperation rate[9,10].

We report our experience using the vertical Silastic® (Dow Corning, Reading, UK) ring gastroplasty as the treatment for morbid obesity.

Patients and methods

All patients were operated on at the General Hospital, Birmingham, UK by one surgeon (R.M B) between July 1981 and January 1987. Seventy-one patients (10 men, 61 women), with a mean age at presentation of 36 years (range 17–56 years) underwent vertical Silastic ring gastroplasty (*Table 1*) Morbid obesity is defined as having an excess body weight of 45 kg or 100 per cent above ideal body weight[11] Selection of patients for weight reducing operations also takes into account major risk factors, i.e diabetes, ischaemic heart disease and endocrine disturbances Seven patients (mean excess weight 39·9 kg, range 34·2–44) underwent gastroplasty because of the debilitating morbidity of their gross obesity

All patients were investigated to exclude endocrine abnormalities and other causes of obesity and underwent psychiatric assessment for suitability for operation. Prophylactic antibiotics and subcutaneous heparin were given peroperatively and the latter continued for 5 days after operation or until the patient was ambulant. Laparotomy was performed through an upper abdominal midline incision with the table tilted 45° foot down. The abdominal wall fat thickness was measured as the vertical height from the linear alba to the skin edge midway between the xiphisternum and umbilicus A 50 ml proximal pouch was formed using a double application of staples from an AutoSuture TA 90® (Auto Suture Company, Ascot, UK) stapling device from which two staples were removed from the lesser curve end Thus a total of four staples was removed from each cartridge together with the corresponding tissue crushing face. Accuracy in size of proximal pouch and stoma was achieved using an inflated 50 ml balloon attached to a nasogastric tube 12 mm in diameter The stoma on the lesser curve was reinforced by encircling it with a 5 cm length of Silastic tubing (*Figure 1*).

The pouch and distal stomach were decompressed after operation using a nasogastric tube positioned to traverse the stoma. Two Redivac® (Biomet Ltd , Bridgend, UK) suction drains were placed in the subcutaneous tissues. These were not removed for at least 7 days to allow drainage of necrotic fat which liquefies by about the 5th day into an 'oil slick' in some patients By the 4th postoperative day most patients were commenced on an 800 calorie liquid diet and converted to solid food at 6 weeks

Patients were followed at 6 and 12 weeks after the operation, then at 3-monthly intervals for 2 years and thereafter 6-monthly They were assessed objectively by the measurement of weight loss. As the aim of treatment is loss of the patient's excess weight, we used the representative percentage of excess weight loss based upon the Metropolitan Life Assurance tables[11] and a reduction of mean Body Mass Index (weight in kilograms/(height in metres)^2); normal range 15–25 kg/m^2)[12]. The former method is recommended by the American Society of Bariatric Surgeons and the latter is increasingly advocated as a standard in nutrition and obesity research

Results

A total of 71 patients underwent the operation, none of whom had had a previous gastric procedure. Of the patients seven (10 per cent) failed to attend at 3 months and were lost to further follow-up despite extensive attempts to contact them. A further nine patients had not attended clinic in the previous year. These have been included in the analysis of the data as information was available from the case notes for a minimum of 2 years following gastroplasty. Follow-up at 1, 3, 5 and 6 years was 87 per cent (62 out of 71), 53 per cent (28 out of 53), 64 per cent (14 out of 22), and 75 per cent (6 out of 8) respectively.

Weight loss

The loss of excess weight and reduction of mean Body Mass Index (BMI) is outlined in *Figures 2* and *3*. Over 60 per cent of the excess weight was lost in the first 12 months and was maintained even at 6 years following gastroplasty. Five patients (7 per cent) failed to lose weight following gastroplasty. Two refused revision; two patients had a large proximal pouch with staples having given way and were converted to gastric banding at reoperation, and one patient who had a tight stenosis with dense adhesions required a gastrogastrostomy. If the seven patients who were lost to follow-up were regarded as treatment failures, our overall failure rate was 17 per cent.

Revisions

Nineteen patients (27 per cent) underwent reoperation following vertical Silastic ring gastroplasty. Three patients (two were converted to gastric banding, one had a gastrogastrostomy) were considered to be treatment failures. Sixteen patients (23 per cent) underwent elective revision for technical complications at a mean of 3·3 years following gastroplasty. Nine

Table 1 *Preoperative characteristics of patients undergoing vertical Silastic ring gastroplasty* (n = 71)

	Mean	Range
Age(years)	36	17 – 56
Original weight(kg)	132	99·3–235
Excess weight(kg)	68	34·2–167
Percentage excess weight	104	47 –247
Body Mass Index(kg/m^2)	49	35·1– 83 3

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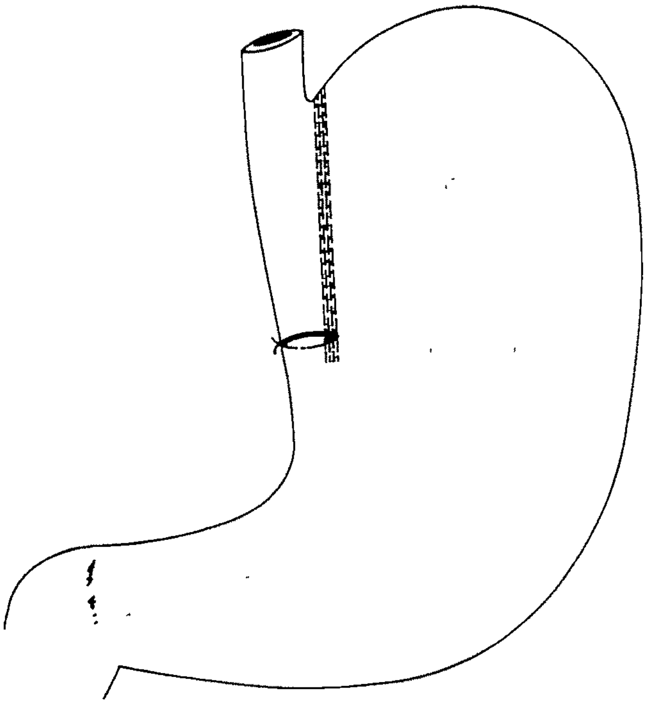

Figure 1 *Vertical Silastic ring gastroplasty Proximal pouch volume 50 ml, 12 mm diameter stoma, supported by a 5 cm Silastic ring*

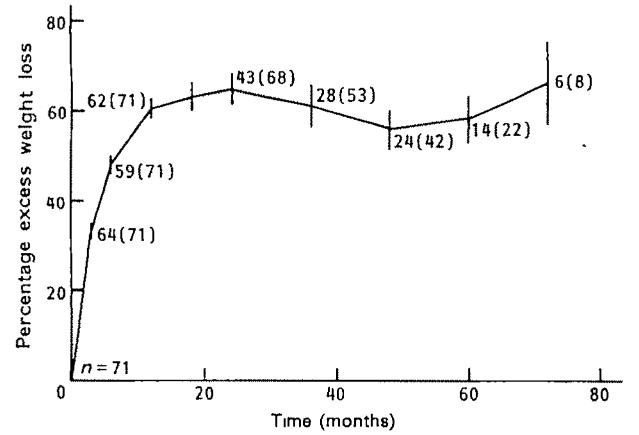

Figure 2 *Percentage excess weight loss* versus *time* n = *number of patients at each time point on whom follow-up data were available, number of patients potentially evaluable is in parentheses, values are mean(s e m)*

patients had moderate to severe vomiting (more than 5 times per day) and were found to have stenosis of the stoma due to a tight Silastic band. These were taken down and replaced. Seven patients had increasing compliance for food and gained weight after initial weight loss. The stoma was found to be too large in one, the Silastic ring having apparently vanished, and a large dilated proximal pouch was found in the remaining six patients. After revision gastroplasty, all patients continued to lose weight over a mean follow-up of 23 months. The percentage excess weight loss at 5 years for the revision group was 60·1 per cent (five patients)

Complications

There were no early or late deaths (*Table 2*).

One patient (original weight 120 kg) needed a gastrostomy for a perforated proximal compartment 9 days after gastroplasty. A week later she required a further laparotomy for oversewing of a perforation of the jejunum. She made a satisfactory recovery.

One patient developed an ileofemoral deep venous thrombosis confirmed by venography. Another patient had a pulmonary embolus confirmed by a ventilation/perfusion scan. Both were treated by conventional anticoagulant therapy.

Wound infection developed in 18 patients (25 per cent) This did not correlate with abdominal wall fat thickness (P = n.s.).

An incisional hernia was noted in 14 patients (20 per cent) at a mean of 2·2 years after gastroplasty.

After satisfactory weight reduction 18 patients (25 per cent) subsequently had abdominal apronectomies for cosmetic reasons

Discussion

Increasing awareness of the failure of conservative treatment to control morbid obesity and the excess mortality and morbidity associated with this disorder have led to the evolution of surgical treatments. Small bowel bypass operations, which carried a high morbidity and a significant mortality[13], were superseded by gastric bypass following the work of Mason in 1966[1]. Gastric partitioning or gastroplasty is a modification of this procedure. The objective of gastroplasty is to preserve a proximal compartment measured at the time of surgery[14], construct a non-expanding stoma and preserve the integrity of the staple line. The primary advantages of gastroplasty are that it is more effective in achieving weight reduction with a lower morbidity and mortality than gastric bypass with none of the metabolic, renal or hepatic problems associated with jejunoileal bypass[15].

We have reported our experience using a more recent variation; the vertical Silastic ring gastroplasty advocated by Echout *et al.*[16]. This is a simpler procedure and offers distinct technical advantages compared with the vertical banded gastroplasty favoured by Mason *et al*[17], which involves the creation of a circular stapled gastric window.

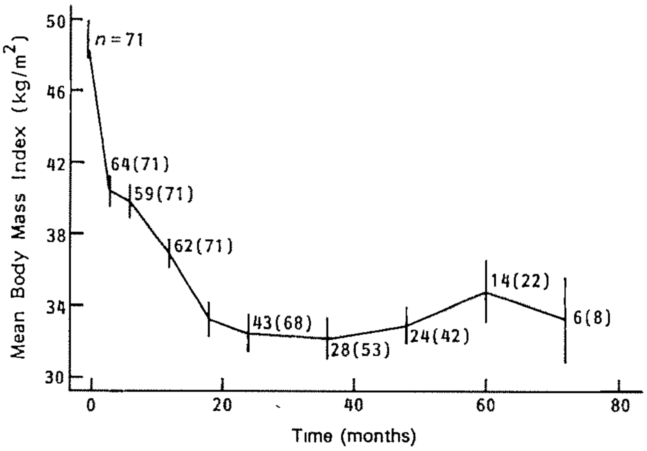

Figure 3 *Mean Body Mass Index* versus *time* n = *number of patients at each time point on whom follow-up data were available, number of patients potentially evaluable is in parentheses, values are mean(s e m.)*

Table 2 *Complications following vertical ring gastroplasty*

Complications	Number of patients (71)	
Failed gastroplasty	5	
Revisions	16	Stenosis/tight band, 9 Large pouch, 6 Large stoma, 1
Deep venous thrombosis	1	
Pulmonary embolus	1	
Peritonitis	1	Perforated proximal compartment and perforated jejunum
Wound infection	18	
Incisional hernia	14	

Vertical Silastic ring gastroplasty has advantages over the horizontal type. It is easier to perform, requires virtually no dissection along the greater curvature of the stomach, therefore reducing the risk of injury to the spleen[4] and of devascularization of the fundal pouch, and is amenable to easier endoscopic assessment. Although weight loss is similar, horizontal stapled gastroplasty has a higher rate of stoma revision[18]. Previous studies for various gastric bypass procedures reported initial good results followed by reports of complications and failure on longer follow-up. Willbanks[19], in a series of 305 morbidly obese patients, reported a loss of mean excess weight of 60·8 per cent at 2 years with 14 patients (5·5 per cent) failing to lose weight following vertical Silastic ring gastroplasty. Our experience, the largest long-term follow-up in the United Kingdom, confirms that vertical Silastic ring gastroplasty is an effective operation in reducing weight.

Of the patients 23 per cent underwent an elective revision procedure in this series The majority were related to stenosis of the stoma on the lesser curve either because of a dense fibrous reaction or a tight Silastic ring. This occurred mainly in the early part of the series. The remainder were due to increased compliance of the proximal pouch resulting in a larger food intake. Despite the high revision rate, subsequent weight was satisfactory. Our failure rate of 7 per cent (17 per cent if non-attenders are included) compares favourably with other groups and other weight reducing operations[20]. It must in part reflect poor patient selection and compliance. Some patients go to extraordinary lengths to consume foods of low volume and high calorific content, emphasizing the need for careful preoperative psychiatric assessment.

The one perioperative complication, perforation of the proximal compartment, was further complicated by perforation of the jejunum a week later. Perforation of the proximal pouch has been extensively reported by Mason *et al.*[21] and is managed by simple closure and gastrostomy. We have reported a wound infection rate of over 25 per cent. Our routine precautions now include prophylactic antibiotics, wound irrigation to remove loose fat tissue, deep tension sutures to embrace the fat layer and Redivac drains to remove the 'oil slick'.

The automatic stapling devices have greatly facilitated the total partitioning of the stomach. The recent availability of the notched TA90 stapler (AutoSuture TA90 BN®, AutoSuture Company, Ascot, UK) has simplified the stapling technique and reduced the length of the operation to 60–75 min. The application of a double row of staples, reinforcement of the stoma by a Silastic ring and adherence to a liquid diet in the first 6 weeks are attempts to prevent staple line dehiscence (two patients in this series). These advances in operative technique, the relatively low morbidity and zero mortality in our series of morbidly obese patients make vertical Silastic ring gastroplasty a safe and simple procedure in the effective management of massive obesity.

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Pancreatic exocrine function after a sutureless pancreatico-jejunostomy following pancreatico-duodenectomy

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Exocrine pancreatic function was measured in 14 patients after pancreaticoduodenectomy for periampullary neoplasms in order to assess the patency of a sutureless pancreatico-enteric anastomosis. Pancreatic function was examined by the p*-aminobenzoic acid/*p*-aminosalicylic acid (PABA/PAS) test 3–160 months after operation and compared with age- and sex-matched controls. There were no significant differences between mean (s.e.m.) serum PABA concentrations 3 h after ingestion of* N*-benzoyl-*L*-tyrosyl-PABA (25·5 (3·6)) μmol/l for patients, 26·1 (2·0) μmol/l for controls). However, the mean (s.e.m.) PABA excretion index was significantly lower in the patients (0·58 (0·08)) than in the controls (0·76 (0·04)). Four patients required pancreatic enzyme supplements for control of diarrhoea. Self-limiting pancreatic leaks occurred in two patients. The results suggest that the sutureless pancreatico-enteric anastomosis has an acceptably low leakage rate but that pancreatic exocrine function is diminished following pancreaticoduodenectomy with this technique. However, the majority of patients require no enzyme supplements and no significant tendency to late stenosis of the anastomosis was demonstrated.*

Keywords: Pancreatectomy, pancreaticojejunostomy, pancreatic insufficiency

Radical pancreaticoduodenectomy has been practised for more than half a century[1] and offers the best prospect of cure to patients with periampullary carcinomas The postoperative mortality rate has been gradually reduced from between 20 and 40 per cent[2–4] to as low as 3 per cent[5]. The procedure is still a formidable one, however, and is associated with significant perioperative morbidity. Pancreatic fistula is the most common postoperative complication and may result in death, sepsis or haemorrhage[5,6]. Optimum management of the pancreatic duct anastomosis is a controversial subject. The objective is to secure a leakproof anastomosis which will not subsequently stenose and produce pancreatitis or exocrine insufficiency

For some years we have employed a sutureless pancreatico-jejunostomy temporarily supported by an indwelling stent. The long-term patency of this anastomosis has until recently been difficult to assess. However, improvements in measurement of pancreatic exocrine function now enable the patency of the pancreatico-enteric anastomosis to be indirectly measured.

Patients and methods

Patients presenting with periampullary carcinomas were treated by pancreaticoduodenectomy Jaundiced patients were managed by endoscopic sphincterotomy and liver function tests were allowed to normalize before operation. The operative technique was the same in each case except that the gallbladder was left *in situ* in some patients. All patients underwent *en bloc* resection of the head of the pancreas, duodenum, gastric antrum and lower bile duct. Reconstruction of the alimentary tract was carried out by bringing the oversewn end of the proximal jejunum through the transverse mesocolon to the supracolic compartment The bile duct and gastric remnant were anastomosed end-to-side to the jejunum. Between these two anastomoses a serosal cut was made in the jejunum corresponding to the cut end of the pancreas. A stab incision was made into the jejunal mucosa. The hub of a soft, 6Fr gauge umbilical catheter (Portex Ltd , Hythe, UK) was then cut off and the cut end passed through the stab incision into the lumen of an 18Fr latex T tube previously placed within the jejunum (*Figure 1*) The other end of the umbilical catheter was passed into the pancreatic duct. The pancreatic capsule was then anastomosed securely to the jejunal serosa with non-absorbable sutures. One limb of the T tube was passed through the bile duct anastomosis and the other through the gastroenterostomy The jejunum was sutured round the emerging stem of the T tube and a leaf of omentum interposed between the jejunum and the parietal peritoneum. After approximately 14 days the T tube was cut short and the umbilical catheter withdrawn. The T tube itself was withdrawn after 21 days.

Pancreatic exocrine function was measured using the modified *p*-aminobenzoic acid/*p*-aminosalicylic acid (PABA/PAS) urine test described by Hoek *et al.*[7] and additional serum PABA levels were measured at 3 h[8]. Any pancreatic supplements were stopped 48 h before the test and the patients fasted overnight. Baseline serum and urine samples were taken and the patients received 1 g *N*-benzoyl-L-tyrosyl-PABA (BTPABA) and 360 mg PAS together with a Lundh meal. A serum sample was taken 3 h later and a 6-h urine sample was collected PABA and PAS concentrations in urine and PABA concentrations in serum were measured by high performance liquid chromatography[7]. The amount of free PABA recovered in urine in 6 h was expressed as a percentage of the PABA ingested orally as BTPABA. A similar calculation was performed for PAS and the ratio of the percentages of PABA PAS was calculated as the PABA excretion index (PEI)

Age- and sex-matched controls were drawn from patients with no history of gastrointestinal disease who were admitted for minor surgical procedures such as hernia repair

Statistical analysis was performed using Student's *t* test and least squares regression analysis

Results

Fourteen consecutive patients who had undergone pancreato-duodenectomy for periampullary neoplasms were studied. The mean (s.e.m.) ages of the patients and controls were 61·6 (2·6) and 59·4 (3·9) respectively. There were six women and eight men in each group. The mean time since operation for the patients was 29 months. Six had undergone surgery within the previous 12 months and eight were studied between 12 and 160 months after operation. Ten patients had been operated on for ampullary carcinomas, two for duodenal carcinoma and one

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for each of common bile duct carcinoma and duodenal villous adenoma.

Two patients drained >100 ml of pancreatic juice per day from the abdominal drains. Both of these leaks resolved during the first 2 postoperative weeks.

Urinary recovery of PABA and PEI were significantly lower in the patients than in the controls (*Table 1*, *Figure 2*). The 3-h serum PABA concentrations were the same in each group. No correlation was observed between the PEI and time after operation ($r = -0{\cdot}08$) or between 3-h serum PABA concentration and time ($r = -0{\cdot}21$). Four patients required pancreatic enzyme supplements for control of diarrhoea. The mean PEI in the patients who required enzyme supplements was 0·44 compared with 0·65 in those who did not. The mean 3-h serum PABA concentration in the supplemented patients was 13·3 μmol/l compared with 30·4 μmol/l in the unsupplemented group.

Discussion

Leakage of pancreatic juice from the pancreaticojejunal anastomosis is the most common cause of postoperative morbidity following pancreaticoduodenectomy[6] and may lead to the death of the patient. A variety of techniques has been described to minimize the possibility of leakage from this anastomosis. The most radical solution to the problem has been to avoid any pancreatico-enteric anastomosis at all by performing total pancreatectomy. This approach is associated with an increased incidence of diabetic complications and morbidity and mortality rates at least as high as the standard procedure despite the absence of any fistula-related complications[5]. A second method for avoiding an anastomosis is to ligate the pancreatic duct and accept the development of exocrine failure. This technique almost always results in fistula formation[6]. Consequently, most pancreatic surgeons attempt to obtain pancreatico-enteric continuity either by invaginating the stump of the pancreas into the jejunal loop or by direct suture of the duct to the intestinal mucosa. The latter technique is particularly difficult when the pancreatic duct is small and a number of authors have described sutureless techniques to facilitate restoration of mucosal continuity[9,10]. For several years we have used a sutureless anastomosis temporarily supported by an indwelling stent. Although this technique is associated with an acceptably low rate of pancreatic fistula formation, there is a risk that the anastomosis might stenose after the stenting tube is removed. Anastomotic occlusion has been observed at post mortem after pancreaticoduodenectomy[9]. In life this may lead to exocrine failure and the need for pancreatic enzyme supplementation. In some series this appears to be a frequent occurrence after pancreaticoduodenectomy[11].

The development of a reliable 'tubeless' test of pancreatic function[7] has provided a non-invasive method which is more

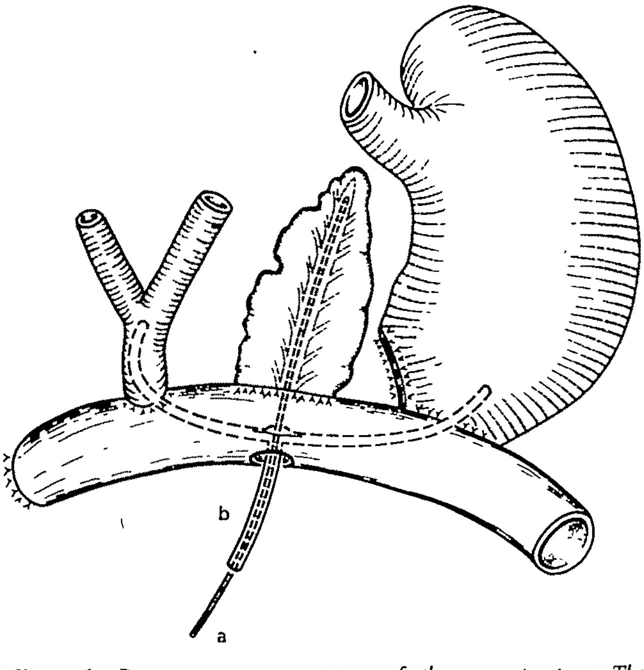

Figure 1 *Diagramatic representation of the reconstruction. The umbilical catheter (a) lies within the lumen of the stem of the T tube (b)*

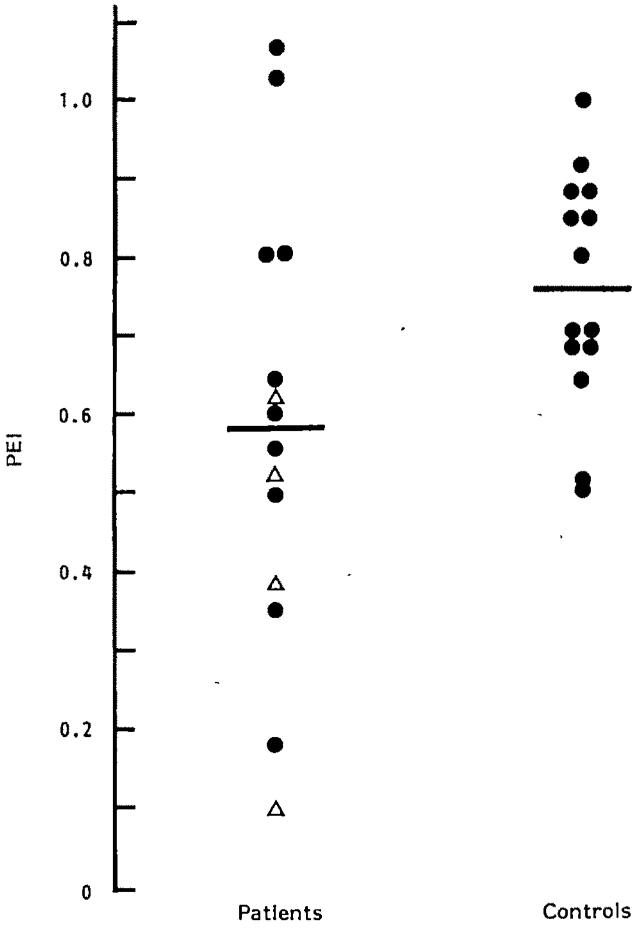

Figure 2 *PABA excretion index in patients and controls. The difference between the two groups is significant at the 5 per cent level. △, Patients who require enzyme supplements*

Table 1 *Exocrine pancreatic function in pancreaticoduodenectomy patients and controls*

Group	*n*	Urine PAS recovery (%)	Urine PABA recovery (%)	PEI	Serum PABA (μmol/l)
Pancreaticoduodenectomy patients	14	66·6 (5·1)	39·7 (6·4)	0·58 (0·08)	25·5 (3·6)
Controls	14	74·8 (3·6)	56·9 (3·5)	0·76 (0·04)	26·1 (2·0)
		n.s.	$P<0{\cdot}05$	$P<0{\cdot}05$	n.s.

Values are mean(s.e.m.) PEI, PABA excretion index; n.s., not significant. *P* values calculated by Student's *t* test sensitive than the presence of steatorrhoea for assessing the exocrine function of the pancreatic remnant[12]. The PABA/PAS test depends upon the hydrolysis of orally ingested BTPABA to PABA by pancreatic proteolytic enzymes Free PABA may then be absorbed from the intestine and is excreted in the urine. PAS has a molecular structure which differs from PABA by only one hydroxyl group and is absorbed and metabolized in a comparable manner to free PABA. The simultaneous measurement of PAS excretion enables variations in gastric emptying and other non-pancreatic factors such as absorption and renal excretion to be compensated for. This is particularly important after pancreaticoduodenectomy where the antrectomy is very likely to modify gastric emptying.

A significant reduction in pancreatic exocrine function was observed after pancreaticoduodenectomy and four patients required regular enzyme supplements The need for pancreatic enzyme replacement was supported by the reduced PEI in these patients compared with the unsupplemented group, and in particular by the 3-h serum PABA concentrations. The reasons for diminished pancreatic function include stenosis of the pancreatico-enteric anastomosis. Early stenosis was seen in one patient in whom the pancreatic stent had drained >500 ml of pancreatic juice per day. Exocrine failure at 3 months was shown by a PEI of 0·25 which had diminished to 0·1 when retested for this study at 9 months A similar reduction in PEI from 0·88 at 3 months to 0·50 at 13 months was seen in a second patient. Late stenosis of the anastomosis probably explains the reduced pancreatic function in some patients even though no correlation was found between pancreatic function and time after operation for the whole group It is also possible that chronic obstruction of the pancreatic duct may lead to reversible fibrous replacement of the exocrine tissue. Previous studies have shown that pancreatic function may take up to a year to recover after pancreaticoduodenectomy, partly because of the effects of preoperative obstruction[13,14]. However, exocrine function returns to nearly normal within 3 months after the obstruction has been relieved in an experimental model[13]. The four patients in this series who required enzyme supplements had undergone surgery 9, 25, 37 and 58 months before the study It is therefore improbable that the reduction in exocrine function was a reversible phenomenon.

The results of this study indicate that a proportion of patients will have biochemical or clinical evidence of pancreatic insufficiency after pancreaticoduodenectomy using the sutureless technique. Nevertheless, the majority of patients require no pancreatic supplements. Only two patients in this series had postoperative pancreatic leaks, both of which resolved spontaneously. These observations suggest that this method of performing pancreatico-enterostomy is safe and effective and is particularly useful when the pancreatic duct is small.

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Evaluation of fine catheter aspiration cytology of the peritoneum as an adjunct to decision making in the acute abdomen

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Fine catheter aspiration cytology of the peritoneal cavity was performed successfully in 61 patients admitted with acute abdominal pain. Aspirates were examined microscopically and the percentage of neutrophils in the specimen counted. In patients in whom the clinical need for operation was certain ($n=25$) *all patients required surgery and the peritoneal neutrophil count was* >50 *per cent. In patients in whom the clinical need for operation was uncertain* ($n=36$) *19 patients required operation: the peritoneal neutrophil count was* >50 *per cent in 18 and in one patient with ectopic pregnancy fresh blood was aspirated. Of the 17 patients not requiring operation the peritoneal neutrophil count was* <10 *per cent in 15 and* >50 *per cent in two patients (both had acute pelvic inflammatory disease). This study confirms peritoneal cytology as a useful adjunct to decision making in those patients with acute abdominal pain in whom the decision to operate is in doubt.*

Keywords: Acute abdomen, cytology, laparoscopy, diagnosis

In the management of the acute abdomen most surgeons, when in doubt, err on the side of caution. Both computer aided diagnosis[1] and laparoscopy[2] have been shown to improve decision making and reduce errors. The former requires expensive equipment and the latter a particular expertise; both are not yet widely used. Peritoneal lavage has also been used in the diagnosis of the non-traumatic acute abdomen but has not been widely applied[3]. A method of examining a cellular exudate aspirated from the peritoneal cavity, where the percentage of neutrophils in the sample is measured, has recently been described[4,5]. We have evaluated the potential role of peritoneal cytology in patients with acute abdominal pain.

Patients and methods

Over a 6-month period all patients admitted under one surgical firm with acute abdominal pain were assigned to one of four groups after clinical evaluation and baseline investigations (full blood count, serum urea and electrolytes, serum amylase, urine microscopy and plain X-ray) (A) definitely requires operation, (B) definitely does not require operation; (C) need for operation uncertain – this group included all women with 'query appendicitis' as the error rate in such patients approaches 40 per cent[6], (D) exclusions from study.

Children under 16 years were excluded because of non-availability of a paediatric laparoscope. Abdominal trauma and inflammatory bowel disease were excluded as they present with distinctive features and require specific evaluation and investigation. Acute pancreatitis and renal tract disease, although non-specific in their presentation, are readily identified by serum amylase and urine microscopy respectively.

Fine catheter aspiration cytology of the peritoneum (FCACP) was performed in groups A and C under general anaesthesia before operation. Group A then proceeded to laparotomy and group C to laparoscopy with or without laparotomy. A final diagnosis was therefore made in all these patients.

FCACP specimens were obtained in a standard fashion. The bladder was emptied by catheterization and, under sterile precautions, a 14 gauge cannula (Abbocath, Abbott, Sligo, Ireland) inserted midway between the umbilicus and pubic symphisis. A 3.5 Ch umbilical artery catheter (Argyle, Petit-Rochain, Belgium), having had the distal 10 cm fenestrated with a 25 gauge needle, was then inserted through the cannula. The fine catheter was manoeuvred throughout the peritoneal cavity while suction was applied with a 10 ml syringe. Before removing the catheter negative pressure was released from the syringe. After removal the syringe was disconnected, filled with air, reattached and the aspirate deposited on a slide. A thin smear was made and the preparation air-dried. Specimens were then delivered to a cytologist and stained by the modified Romanowsky method (Hema Gurr, BDH Ltd., Poole, UK). The cell profile was examined by microscopy (× 400) and peritoneal neutrophil percentage calculated after counting 500 nucleated cells.

The test results were then correlated with the clinical decision and the final diagnosis after either laparotomy or laparoscopy. The study was approved by the local hospital ethical committee. Statistical analysis was by Fisher's exact test.

Results

One hundred and thirty-one patients entered the study from which 32 were excluded (*Table 1*). Thirty-one patients were assigned to group B and none of these patients subsequently required urgent operation. Thus 68 patients were eligible for FCACP and this was successfully performed in 61. The peritoneal neutrophil percentage for these patients is shown in *Figure 1*. In group A ($n=25$) all patients required surgery and the peritoneal neutrophil percentage was >50 per cent in all. In group C ($n=36$) FCACP correctly identified all 19 patients requiring surgery; in 18 the PNP was >50 per cent and in one patient with ectopic pregnancy the aspirate was fresh blood

Table 1 *Exclusions from study*

Contraindications to laparoscopy	
Age <16 years	13
Multiple abdominal operations	1
Severe cardiopulmonary disease	0
Intestinal obstruction	4
Fine catheter aspiration cytology unlikely to be helpful	
Acute pancreatitis	3
Abdominal trauma	4
Renal tract disease	5
Inflammatory bowel disease	2
Total	32

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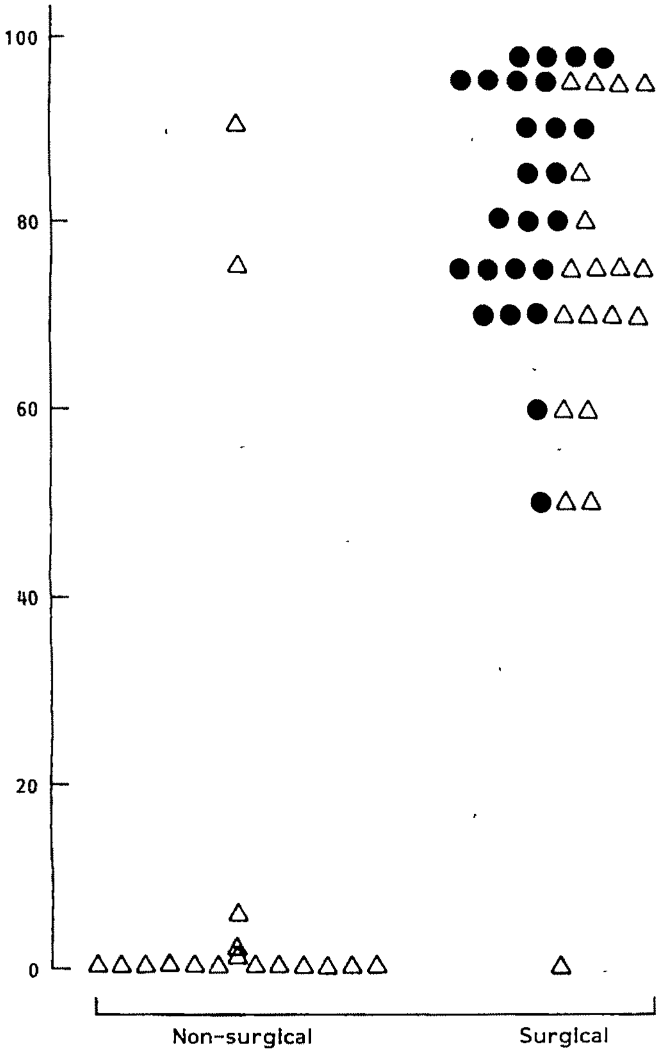

Figure 1 *The peritoneal neutrophil percentage for the non-surgical and surgical acute abdomen* ●, *group A,* △, *group C Non-surgical ovarian cyst, 4, non-specific abdominal pain, 6, pelvic inflammatory disease, 6, retrograde menstruation, 1 Surgical appendicitis, 33, perforated viscus, 6, empyema gallbladder, 2, infected ascites, 1, primary peritonitis, 1, ectopic pregnancy, 1*

establishing the need for operation. There were two false positives – both acute pelvic inflammatory disease. In group C 17 patients did not require surgery and, if FCACP had been used for decision making, it would have reduced unnecessary laparoscopy in this group from 17 of 36 to 2 of 36 patients ($P<0.01$).

Technical failure of FCACP occurred in seven patients; in three patients obesity prevented the cannula reaching the peritoneal cavity and in four patients the aspirate was acellular These failures were all recognized at the time of the test and all these patients were subsequently found to have acute appendicitis Including these failures, which are regarded as false negatives, the test sensitivity is 86 per cent, specificity 88 per cent, the predictive value of a positive test 96 per cent and of a negative test 68 per cent. There were no complications of FCACP during this study.

Discussion

This study confirms that FCACP is a sensitive and specific indicator of acute intra-abdominal inflammation when the peritoneal neutrophil percentage is >50 per cent. The test is obviously unable to identify the cause of the underlying inflammatory disorder for which laparotomy is not always required The elimination of technical errors would raise the predictive value of a negative test. With good decision making the benefit of FCACP is restricted to the 'uncertain group'. We suggest that FCACP be applied in this group, if the result is positive then the patient should proceed to laparotomy unless pelvic inflammatory disease is a possibility in which case laparoscopy is required.

FCACP is an inexpensive and quick technique; the procedure and staining of the smear as described takes approximately 15 min and may be performed under local anaesthesia. Recognition of the neutrophil is straightforward and interpretation can be performed by the receiving clinician or a technician 'out of hours'. The results of this study indicate that selective use of FCACP in the manner described can lead to accurate recognition of surgical disease and appropriate treatment.

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Role of compartmental resection for soft tissue sarcoma of the limb and limb girdle

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A total of 143 consecutive operations for soft tissue sarcoma of the extremity, performed by one surgeon over a 5-year period, was studied to determine the place of compartmental excision. The surgical aim was to achieve the nearest to radical surgery compatible with preservation of a functional limb. Of the operations, 73 were for previously untreated primary tumour and 70 for local recurrence. Two tumours arose in areas previously irradiated for other malignancies and 35 recurrences had occurred despite prior radiotherapy; of the 106 remaining cases, adjuvant radiotherapy was used for 79. Adjuvant chemotherapy was used only occasionally and was more often regional than systemic. For the majority of tumours, compartmentectomy was inappropriate or inadequate: 49 were extracompartmental in origin and 48 extended beyond their compartment of origin at the time of surgery. The remaining 46 were confined to one compartment; in only 21 of these 46 operations was a radical compartmental excision performed. Compartmental excision was more likely to be performed when the tumour was centrally located within a compartment, was so large that it replaced most of the muscle group, or was high grade or recurrent (particularly when adjuvant radiotherapy had already been used). The general preference was to combine less-than-radical surgery with adjuvant radiotherapy rather than sacrifice entire muscle groups or adjacent, functionally important, structures such as artery or nerve. This reflects the proven efficacy of radiotherapy in controlling microscopic disease. Overall, compartmental excision was considered appropriate in only 15 per cent of operations.

Keywords: Soft tissue neoplasm, sarcoma, surgery

When developing within muscle groups, soft tissue sarcomas of the limb and limb girdle spread both in continuity and in the form of 'skip lesions' (tumour foci separate from the main bulk), initially confined within the muscle of origin The main tumour and any skip lesions are, therefore, generally removed if the entire muscle compartment containing the tumour is excised. Good local control was obtained in early series by means of radical amputation, transecting the limb level with or above the origin of the musculofascial compartment containing the tumour. Subsequently the less mutilating operation of radical, compartmental excision was developed as a good alternative to amputation for appropriate soft tissue sarcomas[1,2]. This form of operation, in which the entire musculofascial compartment containing the tumour is resected, leaves a limb with altered but usually acceptable function, and was considered the optimal procedure when no form of treatment adjuvant to surgery was available. Soft tissue sarcoma was originally believed to be radioresistant. Adjuvant radiotherapy has now been proven to be effective in treating the microscopic disease which remains after excision with narrow clearance margins[3]. The place of compartmental excision might therefore be expected to be more limited now.

To determine how often compartmental excision was considered appropriate for limb and limb girdle soft tissue sarcoma we studied a consecutive series of 143 operations in patients referred to one surgeon. (G.W.). We first identified those tumours for which compartmentectomy was feasible and then investigated the circumstances in which it was used.

Patients and methods

Over the 5-year period from May 1982 to April 1987, 126 patients with soft tissue sarcoma of the limb or limb girdle (*Table 1*) had surgery at the Royal Marsden Hospital Histological confirmation of the diagnosis was obtained in every case and in most cases tissue was available for subsequent review and grading of degree of malignancy (*Table 2*) Benign lesions, desmoid tumours, fibromatosis and embryonal tumours were excluded from consideration.

One hundred and forty-three operations were studied (seven patients had two operations, one had three and two had five). Of these 73 were performed as the first definitive surgical treatment of the primary tumour; 70 were carried out for tumour recurrences. Of the primary tumours, 31 had been referred after excision biopsy, and re-excision was performed. The surgical aim was to achieve the nearest to radical surgery compatible with preservation of a functional limb.

To determine the exact tumour location relative to musculofascial boundaries we used a combination of the preoperative clinical description of the tumour, the computed tomographic scan, the operative note and the detailed pathological description of the operative specimen In the majority of cases the excision margin was stated in the operative description and in the histopathological report. When a measurement was not given an estimate could be obtained from the description of operation and specimen. No attempt was made to correct for tissue shrinkage with fixation. The extent of surgery was defined according to Enneking and colleagues[1,2] Surgery in which the plane of excision was through tumour was categorized as intracapsular. If tumour and pseudocapsule only were excised, the excision was called 'marginal' The acceptable margin for 'wide' excision depends on the site. a 3 cm margin is realistic in the thigh but rarely in the distal extremities We therefore used the term 'wide' to describe excision with a greater than 1 cm margin of clearance. A radical excision was one in which the entire musculofascial compartment containing the tumour was excised, regardless of the measured excision margin

Adjuvant radiotherapy was used when excision margins were small and/or the tumour was high grade. This applied to 54 of the 73 operations for previously untreated tumour and 25 of the 70 operations for soft tissue recurrence (*Figure 1*). All radiotherapy was given by

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Table 1 *Tumour sites of 126 patients*

Buttock	Inguinal region	Thigh	Knee	Leg	Ankle	Foot	Shoulder	Axilla	Upper arm	Elbow	Forearm	Write	Hand
6	11	55	4	10	1	3	6	6	8	5	8	1	2

Table 2 *Histological diagnoses and grades of 126 tumours, excised at 143 operations*

	Grade			
Diagnosis	High	Low	Unknown	Total
Extraosseous chondrosarcoma		1		1
Dermatofibrosarcoma		1		1
Epithelioid sarcoma	4			4
Fibrosarcoma	1	2		3
Malignant fibrous histiocytoma	27	18	2	47
Haemangiosarcoma		2		2
Leiomyosarcoma	3	1		4
Liposarcoma	5	23	1	29
Malignant nerve sheath tumour	2	3		5
Rhabdomyosarcoma	5			5
Synovial sarcoma	16			16
Undifferentiated sarcoma	9			9
Totals	72	51	3	126

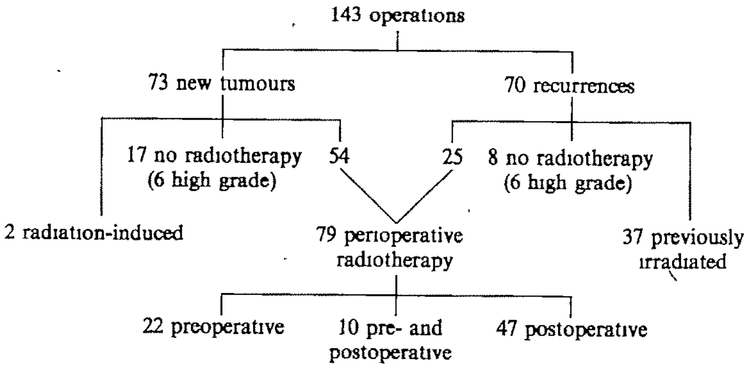

Figure 1 *Relationship of adjuvant radiotherapy to operative treatment of new tumours and recurrences*

external beam; no implants were used The median treatment dose was 60 Gy, usually given in daily 2 Gy fractions over 5 days per week for 6 weeks Preoperative radiotherapy was used for large, clinically fixed, tumours and during a pilot study with intra-arterial doxorubicin, as described later Of the patients 22 were irradiated preoperatively, 47 postoperatively and ten patients had a split course of therapy Of the primary tumours in the study group, two were in areas previously irradiated and were considered to be radiation-induced In 35 of the 70 operations for recurrent tumour, radiotherapy had been used as part of the treatment of earlier disease; no further irradiation was given in these circumstances

Nine patients with primary tumours and six with local recurrence were treated, as part of a pilot study, with intra-arterial doxorubicin infusion over 3 days up to a total dose of 90 mg (depending on the region infused), followed by radical radiotherapy and surgery. Adjuvant systemic chemotherapy was not used routinely· three patients with aggressive primary tumours, one with synchronous primary and lymph node disease and two presenting with primary tumour and lung metastases received at least one course of systemic chemotherapy.

The age and sex of the patient, the presence of involved lymph nodes or metastases, the presence of other medical disorders which might have influenced the choice of operation, and any subsequent local recurrence were also determined in relation to each operation.

Statistical significance of observed differences was determined using χ^2 tests to compare numbers of events

Results

Extracompartmental origin

Forty-nine tumours arose in areas not confined by fascial boundaries (*Table 3*); resections in these patients included two amputations.

Transcompartmental extension

Forty-eight tumours extended beyond their compartment of origin; six of these were treated by amputation.

Intracompartmental tumours

Forty-six tumours were confined to the compartment of origin at the time of surgery and compartmental excision was in theory feasible; none was treated by amputation. In only 21 of these patients was complete compartmental excision performed (group I), while in 25 cases less than the entire compartment of origin was resected (group II).

Groups I and II are compared in *Table 4*. With the small numbers in each there were no statistically significant differences between the two groups in the distribution of any variable The proportion given adjuvant chemotherapy or radiotherapy was similar and the outcome, with one local recurrence in each group over comparable time periods, was the same. However, several points of interest were identified:

1. Tumours treated by compartmental excision tended to be large, relative to their compartment of origin, and centrally located. Excluding the lipoma-like liposarcomas, a clearance margin greater than 1 cm was achieved in more operations that were not compartmentectomies (13/21) than in those that were (10/21), reflecting the fact that radically-excised tumours were often those that nearly replaced their compartment of origin. Of 34 thigh tumours 21 were not radically excised; 15 of the total of 18 located in the anterior thigh, where muscle bulk is greatest, did not undergo total compartment resection; only very large tumours could fill the compartment at this site. Of 11 tumours located near the edge of a compartment, only three were radically excised. Of the eight that were not radically resected, six were in the thigh and four of these were located at the medial or lateral edge of the anterior compartment; excision was performed leaving enough muscle at the opposite side to preserve knee stability

2. Recurrent tumour was more likely to have been radically excised. Six of nine recurrent tumours were managed by compartmentectomy, compared with 15 of 37 primary tumours. Of the six recurrent tumours in group I, two were in areas irradiated at the time of treatment of the original tumour. The one tumour that was recurrent after radiotherapy and not radically excised was expanding the proximal limit of the adductor compartment; excising the distal limits of the compartment would not have constituted a better cancer operation

3. Low grade tumours were less likely to be radically excised. Fourteen of the 21 low grade tumours confined to one compartment were not radically resected. These included the four lipoma-like liposarcomas with their low risk of both local recurrence and metastasis. The seven low grade tumours that were excised with their entire containing compartment averaged 11·3 cm diameter. The smallest of these, at 5 cm diameter, was located in the triceps muscle and could not have been excised with a clear margin if any of the compartment had been retained.

Table 3 *Sites of origin of the 49 extracompartmental tumours*

Superficial to deep fascia	26
Femoral triangle	13
Axilla	6
Antecubital fossa	2
Popliteal fossa	2
Total	49

4. Minimal excision margins were used in the forearm. Of the eight forearm tumours in this series two were confined to a single musculofascial compartment. These were not radically excised; excision was wide or marginal, preserving some forearm muscle together with the important neurovascular structures

5. Women were less likely to present with disease confined to one compartment. Comparison of groups I and II shows a similar proportion of women in each group, however 13 (28 per cent) of the 46 patients who had tumour confined to one compartment were female whereas 79 (42 per cent) of the total 187 patients with primary tumours of an extremity seen over the study period were female. Overall there was a statistically significant tendency for men to have treatment with better surgical margins (wide or radical excision) than women.

Discussion

One-third of the tumours studied arose in the subcutaneous tissues or the spaces adjacent to major joints (axilla, antecubital fossa, groin and popliteal fossa). These tumours have no anatomical boundary to restrict growth in the axial direction; they are excised with a wide margin at best. Another third originated within a musculofascial compartment, but presented after spreading beyond its confines and required more than excision of a single compartment. The remaining one-third of tumours could have been treated by compartmentectomy, as found by others[2].

While the 'ideal' soft tissue tumour sits centrally within a large bulk of muscle so that excision of the compartment results in a generous tumour clearance in all directions, in reality tumours may be at one margin, adjacent to or even invading the fascial boundary of a compartment, such that compartmental excision achieves only a marginal clearance at best. In these circumstances, removal of functionally-important tissue many centimetres away from the tumour, on the opposite side of the compartment, is likely to be inappropriate Some compartmental boundaries will restrict tumour growth more

Table 4 *Comparison of variables relating to the operations in which radical (group I) or less than radical (group II) resections were performed for tumours confined to one muscolofascial compartment, four patients with lipoma-like liposarcomas which were not radically excised (a subset of group II) are described in the right hand-column*

Variable	Compartmentectomy performed (group I, $n=21$)	Compartmentectomy not performed (group II, $n=25$)	Lipoma-like liposarcoma (4 of the 25 in group II)
Age (years) range	19–74	17–76	18–67
median	58	60	
Male sex	16	17	2
Concurrent medical conditions	6	5	0
Primary or recurrence	6 recurrent	3 recurrent	0 recurrent
Lymph node involvement	0	3 (2 confirmed by pathology)	0
Metastases	1	0	0
Low grade	7 (1 unknown)	14 (2 unknown)	4
Size (cm) range	1·6–16	0·9–35	20–35
median	10	10	
Thigh site	13	21	4
Excision margin ⩽1 cm	11	11	3
Adjuvant chemotherapy	2 (i-a)	3 (2 i-a; 1 systemic)	0
Adjuvant radiotherapy	18	17	0
Subsequent local recurrence	1	1	0
Median follow-up (weeks)	77	92	

i-a, intra-arterial doxorubicin

effectively than others A narrow measured margin can be truly radical if there is a good barrier such as the fascia lata Less confidence can be placed in a flimsy intermuscular septum, perforated by vessels. There are also sites at which functional muscle groups are not separated by a fascial septum at all. An important example of this is provided by the composite adductor magnus muscle of which the hamstring portion lies in the posterior thigh compartment and the adductor part in the medial compartment. There is no fascial layer between the two parts of this muscle. The boundaries of a compartment will clearly have different implications for tumour containment depending on the local anatomy

Our results indicated that men are more likely to present with disease confined to one compartment, so that they are more commonly candidates for radical resection This may simply be a consequence of larger muscle bulk in men compared with women. The use of narrower excision margins in women may also reflect a desire to minimize deformity.

Despite the fact that the surgical aim was to achieve as close to a radical resection as was compatible with satisfactory limb function, only 15 per cent of patients had a complete compartmental resection. The key to this apparent anomaly is the use of adjuvant radiotherapy which, during the course of the period studied, has emerged as an effective means of controlling microscopic residual disease without unacceptable morbidity.

The definitive series demonstrating better local control from compartmental excision than from more limited forms of limb-conserving resection came from a unit in which adjuvant radiotherapy was not used until quite recently[1,2,4]. While Enneking and colleagues were establishing surgical treatment principles, other departments were studying the combination of surgery and radiotherapy[3,5–13]. Tepper and Suit[9] and Suit *et al.*[14,15], for example, obtained excellent results using careful radiotherapy followed by surgery, often limited to no more than complete removal of macroscopic tumour. Although direct comparison of results from different centres is difficult, particularly in a disease as heterogeneous as soft tissue sarcoma, such results were difficult to discount and there is now good evidence from a randomized, controlled trial that adjuvant radiotherapy is effective in improving local tumour control[3].

Radiotherapy to the limbs and limb girdles must be carefully administered to ensure efficacy while limiting complications. The fields need to include all scars and drain sites and a wide margin around the tumour bed, including the length of the original compartment if the tumour was intracompartmental. At the same time, a part of the circumference of a limb must be spared to allow adequate lymphatic drainage and to avoid long-term distal oedema, and irradiation of joints should be minimized to prevent stiffness and loss of range of movement All such requirements are now well established, and good functional results can be obtained in experienced departments even in difficult areas such as the hand and foot[16–18]. The option of using adjuvant radiotherapy as an alternative to more extensive resection is attractive if the functional and cosmetic loss due to radiotherapy after limited surgery is less than that resulting from more extensive surgery In the forearm, or in any compartment containing a major nerve, the functional advantages of limited surgery and radiotherapy are clear[19]. Radiotherapy achieves poor local tumour control if it is used in the presence of macroscopic disease[20–22]. Complete tumour excision is therefore the minimum surgery required A 'shell out' is not adequate, after initial tumour excision performed in ignorance of the pathological diagnosis, half the wounds contain macroscopic tumour at reoperation[23]. When important structures must be sacrificed to obtain negative margins, reconstruction is often possible[24] and amputation may still be avoided.

Adjuvant chemotherapy has recently become part of soft tissue sarcoma treatment in many centres, with the primary aim of achieving better systemic control There is as yet little published evidence that systemic chemotherapy contributes to local tumour control[8,11,25–28], though the recent European organization for the Research and Treatment of Cancer adjuvant study showed improved local control without survival benefit for head, neck or trunk tumours[29]. Regional chemotherapy may have some value: it shrinks tumour, causes necrosis and is believed to reduce local recurrence[27,30,31] However, regional chemotherapy has not been subjected to controlled prospective trial; it also has its own morbidity and may increase the risk of radiotherapy complications, particularly when doxorubicin is used. This morbidity was confirmed in the patients included in our pilot study of intra-arterial doxorubicin. At present we do not feel that the evidence for benefit is sufficiently compelling to justify routine use of either regional or systemic adjuvant chemotherapy[25,32,33].

In summary, complete compartmental excision is claimed to give the best local control of soft tissue sarcoma because it combines wide clearance with the natural barrier of a fascial boundary When adjuvant radiotherapy cannot be given: for radiation-induced sarcomas, recurrences after radiotherapy, and patients treated in areas with no access to radiotherapy, compartmental excision is the limb-conserving treatment most likely to achieve local control However, compartmentectomy may be attended by a significant morbidity, depending on the site. In the medial and posterior thigh or the upper arm all the muscle can be sacrificed with little functional deficit, whereas in the forearm and hand this is not true. Even high grade tumours, particularly those adjacent to functionally important structures such as a major nerve or artery, in areas which can be irradiated, may not be best treated by compartmental excision, which may often also be unnecessary for tumours that are low grade, small or eccentrically placed within a compartment.

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Photodynamic therapy for colorectal cancer: a quantitative pilot study

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Ten patients with colorectal cancers unsuitable for operation were treated with endoscopic photodynamic therapy (PDT). The patients were assessed before treatment, and at 1 week and 1 month after treatment by colonoscopy with biopsy and endoluminal ultrasound examination. The depth of tumour was measured and the effect of PDT was quantified by measuring the reduction in tumour depth. All patients were sensitized with 2·5 mg kg^{-1} of haematoporphyrin derivative, 48 h before phototherapy. A standard treatment protocol of light exposure was used. Up to four parts of the tumour were treated with 50 J of red light (630 nm) from a tuneable dye laser, through a flexible optical fibre passed through the colonoscope and inserted into the tumour. Two patients with small lesions are tumour-free 20 and 28 months after PDT. One treatment of an advanced tumour was complicated by a haemodynamically significant secondary haemorrhage. PDT may be most suitable for the treatment of small tumours or for small areas of persistent tumour where the bulk has been removed by alternative techniques.

Keywords: Photodynamic therapy, colorectal cancer, laser, endoscopic ultrasound

In the last few years interest has developed in photodynamic therapy (PDT) as a method with potential for the selective destruction of malignant tumours It is based on the systemic administration of photosensitizing drugs that are retained with some selectivity in tumours when compared with the normal tissue in which the tumour arose. When activated by light of the appropriate wavelength, usually from a laser, a cytotoxic effect which can lead to local necrosis occurs in the area exposed to the light.

We have shown by careful adjustment of the photosensitizer concentration that it is possible to destroy experimental colon cancers without producing any damage to adjacent normal colon exposed to similar light doses[1]. This occurs because of photosensitizer photodegradation[2] True selective tumour necrosis occurs to a depth of 1–2 mm. Greater depth of tumour necrosis is possible using higher doses of photosensitizer, but one must then either limit the light exposure to the tumour only, or be able to accept some necrosis in normal areas Some necrosis in normal areas is acceptable as there is a biological advantage in the nature of the damage and healing process in the colon following PDT compared with other methods of local tissue destruction[3]. Photodynamic therapy of normal colon can cause full thickness necrosis without risk of perforation or a decrease in the mechanical strength of the bowel, and healing proceeds with regeneration of all layers of the bowel wall. In contrast, full thickness thermal necrosis of comparable extent is associated with a 22 per cent perforation rate and considerable weakening of the bowel wall[4]. Experimental tumours undergoing necrosis caused by PDT slough and the defect heals by regeneration of normal colon[1].

Following these experimental results, we have performed a pilot study on the efficacy of PDT in a series of ten patients with inoperable colorectal cancer We did not attempt to achieve true selective tumour necrosis, but used larger doses of the photosensitizer to produce greater depth of necrosis. The light was directed principally to neoplastic areas, but adjacent normal areas were exposed to some light to ensure that adequate light doses reached the region where normal and neoplastic tissue met. Since our experimental studies had indicated safe healing following necrosis in such normal areas, this was considered to be justified. To date the vast majority of clinical studies of PDT have failed to measure the effect quantitatively, and treatment has been purely empirical. It is important to be able to predict how much tumour necrosis will be produced with given doses of light and photosensitizer, and to match this to the extent of the tumour. We assessed the tumour response quantitatively by using endoluminal ultrasound, to allow predictive dosimetric calculations for future studies

Patients and methods

Photosensitizer and laser

The photosensitizer used was haematoporphyrin derivative (HpD), synthesized and supplied by Paisley Biochemicals Ltd (Paisley, UK) It contained 44 per cent dihaematoporphyrin ether/ester, considered to be the active component of HpD[5] The patients were admitted to hospital and 2 5 mg kg^{-1} HpD was administered as an intravenous infusion in normal saline over 30 min[6]

Irradiation was performed using a continuous wave argon ion pumped dye laser tuned to deliver light at 630 nm coupled to a 400 μm quartz optical fibre (Living Technology Ltd., Glasgow, UK)

Patients

Ten patients (five men, five women) with a mean age of 73 (range 44–90) years were treated; the patient details are shown in *Table 1*. Patient 1 had had a previous anterior resection and had developed a true anastomotic recurrence with no evidence of tumour invading from outside Patient 8 had a large tumour in the descending colon (68 cm from the renal verge). He was initially treated with high power external, and low power interstitial, Nd YAG laser therapy which reduced the polypoid carcinoma to a small area of residual intramural tumour. Further thermal laser therapy would have risked weakening the colonic wall and producing perforation, endosonography having shown that the tumour was invading the full thickness of the bowel wall. PDT was used to eradicate the residual tumour without risk of weakening the colonic wall

Tumour assessment

All tumours were biopsy proven adenocarcinomas which were predominantly exophytic. In four patients the tumour was completely

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Table 1 *Details of the patients and tumours*

Patient	Reason for inoperability	Tumour site (cm from anus)
1	Recent myocardial infarction Recurrence after anterior resection	10–11 5
2	Metastases, debility	8–12
3	Metastases	8–13
4	Refused surgery	13–17
5	Cardiovascular disease	18–21
6	Cardiorespiratory disease	6–11
7	Metastases, cardiac disease	3–6
8	Cardiomyopathy, general debility. Residual tumour after Nd YAG laser therapy	68–70
9	Cerebrovascular disease, general debility	30–32
10	Metastases	21–24

circumferential The longitudinal extent of the tumour was assessed by sigmoidoscopy All tumours were 5 cm in length or less If greater than this, eradication with PDT was considered to be difficult, and the dangers of secondary haemorrhage significant[7]. Palliative treatment was then considered to be most appropriately performed with the Nd YAG laser The maximum depth of invasion of the tumour was measured using the rectal ultrasound endoprobe type 1846 (Bruel and Kjaer, Naerum, Denmark) with either a 5 5 MHz or 7 0 MHz 90° transducer (focal lengths of 1–4 cm and 2–5 cm respectively). The method of examination was as described by Beynon *et al.*[8] The examination was recorded on video tape and the position of the depth measurements was recorded to ensure accurate follow-up By taking the area of maximum depth of tumour before and after treatment, it was possible to calculate the amount of tumour removed. Ultrasound examination was not possible in one patient with a stenotic tumour The two tumours, 30 and 68 cm from the anal margin, were inaccessible to the rigid rectal probe so assessment was made using the Olympus flexible endoscopic ultrasound (GIF-UM2, Key Med, Southend, UK) Measurements were taken immediately before treatment and 1 week, 3 weeks and 4 weeks after treatment

Method of treatment

Before phototherapy the patients received a rectal washout Those with colonic tumours were given a bowel preparation with sodium picosulphate and magnesium citrate (Picolax®, Nordic Pharmaceuticals Ltd., Feltham, UK) All were treated 48 h after HpD injection, the time considered to give the best therapeutic ratio between tumour and normal tissue[6] The procedure was performed through a colonoscope Sedation with 4–10 mg midazolam (Hypnovel®, Roche Products Ltd , Welwyn Garden City, UK) was only given if the patient was anxious or found the long exposure times uncomfortable. The laser was set to deliver 50–100 mW from the tip of the optical fibre, thus avoiding thermal damage[3] The end of the optical fibre was cleaved to ensure a circular output, and the outer cladding was removed for 1 mm from the fibre tip It was then passed down the instrumentation channel of the colonoscope and inserted 1 mm into the tumour (i e. up to the point where the cladding had been removed) This interstitial method of light delivery was found to provide the best means of illumination Surface irradiation of rectal tumours was difficult as it was hard to hold the fibre in a constant position during bowel movements, also mucus, blood or faeces were likely to cover the tumour and reduce the useful delivered light dose The exposure time used at each treatment point was 500–1000 s, giving an energy of 50 J. It must be emphasized that the choice of treatment parameters was empirical, although our data from experimental studies indicated that these parameters should produce safe tumour necrosis. Reports of previous human studies give no indication of the precise extent of necrosis that might be expected from each treatment point It was one of the aims of this study to quantify this In patients with circumferential tumours up to four areas of the tumour were treated, the same light dose being delivered to each In these tumours the area where the maximum depth of invasion had been measured was treated, and other treatment sites were in separate tumour nodules, such that the light fields just overlapped (*Figure 1*) In large polyploid tumours the four sites of treatment were again in the bulky part of the tumour.

All patients were advised to avoid direct sunlight for 1 month after injection of HpD, and to wear a wide brimmed hat and gloves if going out in the sunlight If following PDT there were still areas of tumour remaining and the treatment had failed to provide adequate symptomatic relief, the patients were treated with the Nd YAG laser[9]

Results

Patient 1, who had a small recurrent anastomotic tumour (maximum depth 6 mm, length 15 mm) 10 cm from the anal margin, was treated at three sites. There was necrotic tumour present 1 week after treatment and by 4 weeks there was no evidence of tumour either at endoscopic examination and biopsy, or at endosonography This patient is disease-free 28 months after treatment. *Figure 2* shows a photomicrograph of the tumour prior to treatment and *Figure 3* is a biopsy from

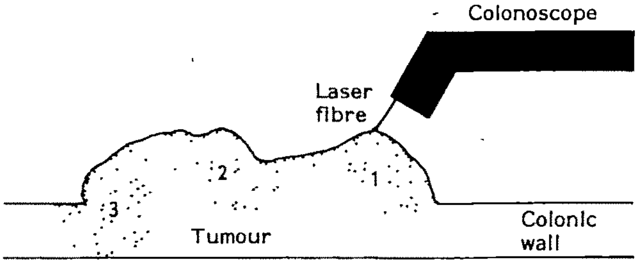

Figure 1 *Diagram of the method of treatment of a longitudinal spreading tumour of the colon, through the colonoscope with the laser fibre inserted into the tumour nodules Three minimally overlapping light fields are shown*

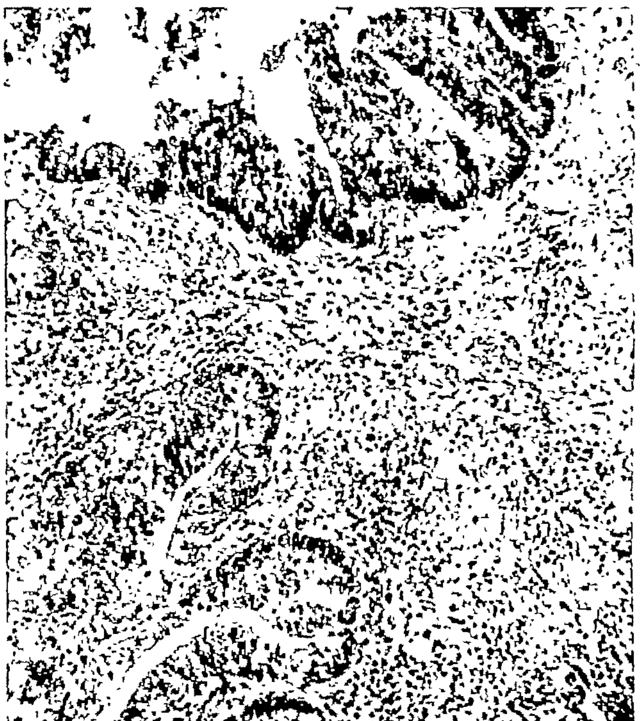

Figure 2 *Photomicrograph of biopsy from colon of patient 1 (adenocarcinoma), haematoxylin and eosin stain, magnification × 100*

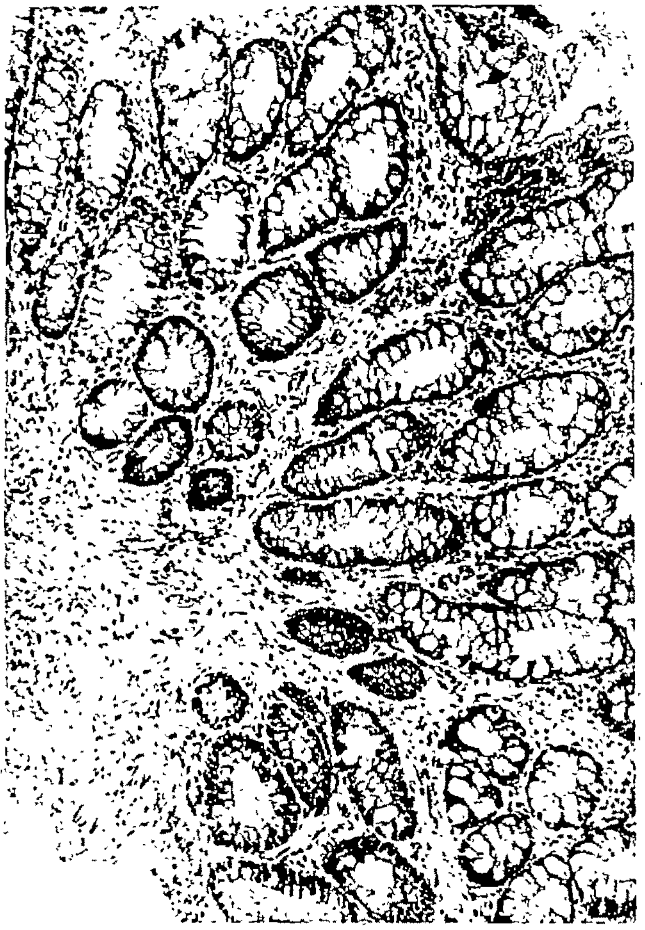

Figure 3 *Photomicrograph of biopsy from the colon of patient 1 showing colonic mucosal regeneration at site of adenocarcinoma, haematoxylin and eosin stain, magnification × 100*

the area 1 month after treatment showing that the colonic mucosa has completely regenerated. Patient 8 had his residual tumour completely eradicated, and he is disease-free 20 months after PDT. A further patient was thought, at colonoscopy, to have tumour completely eradicated 4 weeks after PDT although technical problems prevented satisfactory ultrasound examination. Four months later an intraluminal nodule was noticed a little distance from the site of previous treatment and was found to be a recurrent adenocarcinoma. This recurrence was in an area near the treated tumour, which had not been exposed to the light during treatment.

In eight patients it was possible to measure the depth of tumour invasion before and 1 week after treatment. The results are shown in *Table 2*. The symptomatic improvement at the 1 month follow-up in all patients is shown in *Table 3*. The two patients who had small tumours completely eradicated became asymptomatic. Six patients have died from malignant disease 1, 2, 2, 6, 12 and 15 months after treatment. One patient died from cardiorespiratory disease, 8 months after PDT, and one patient is alive receiving Nd YAG laser therapy (16 months).

Two patients developed complications following PDT. Patient 7, with a large tumour, had a haemodynamically significant haemorrhage from the residual rectal cancer, causing hypotension, and required transfusion with 2 units of blood, 8 days after PDT. The bleeding stopped spontaneously. On examination there had been extensive tumour necrosis exposing friable tumour vessels, that bled easily on contact. We have not treated any more large tumours because of the risk of haemorrhage. One other patient developed mild erythema on one arm when she left it exposed in bright sunlight for 2 h, 4 days after photosensitization.

Discussion

The best results in this series were obtained when the tumour was small and could be totally eradicated. Of the two patients in whom the tumour was completely destroyed, one had a small true anastomotic recurrence and the other had a small area of residual tumour after the bulk had been removed with the Nd YAG laser. These patients illustrate the important biological advantages of PDT. First, the risk of perforation is small even if full thickness necrosis is produced to eradicate the tumour[3,4]. Second, areas of PDT necrosis heal predominantly by regeneration with little scarring[3]. In contrast perforation and severe scarring resulting in stricture formation have occured after Nd YAG laser therapy[10]. The major disadvantage of PDT is that the amount of tumour destruction is limited by the penetration of 630 nm light[11]. Improved light delivery, such as cylindrical rather than point source irradiation, multiple fibre irradiation, and precise placement of the fibres may increase the amount of tumour removed. However, other methods of local tumour destruction with high power, and low power interstitial, Nd YAG laser hyperthermia will produce larger amounts of tumour necrosis since the infrared beam (1064 nm) penetrates further into tissue[11]. These thermal methods are also unlikely to produce haemorrhage. One of our patients had a haemodynamically significant haemorrhage 8 days after PDT. This complication was first reported in a series from the Mayo clinic. Ten patients with bronchial carcinomas were treated with PDT. Two patients with large advanced tumours had major intrabronchial haemorrhage 6 and 11 days after PDT,

Table 2 *Maximum depth of invasion before photodynamic therapy and 1 week after treatment*

Patient	Maximum depth of tumour before PDT (mm)	Maximum depth of tumour after PDT (mm)	Depth of tumour removed (mm)
1	6	0	6
2	16	11	5
3	12	5	7
4	31	28	3
5	26	20	6
6	20	17	3
7	35	20	15
8	4	0	4

PDT, photodynamic therapy

Table 3 *Symptomatic response of patients treated with photodynamic therapy*

Patient	*Symptoms at referral*	*Symptoms after PDT*
1	*Very occasional rectal bleeding*	*No bleeding*
2	*Constipation and overflow diarrhoea Abdominal colic (obstructing tumour)*	*Bowels open daily. No colic*
3	*Constipation and bleeding (obstructing tumour)*	*Constipation improved*
4	*Diarrhoea 3–4 times a day*	No improvement
5	Intermittent diarrhoea	Bowel habit more regular
6	Bowels open hourly. Tenesmus	Very little improvement. Tenesmus not improved
7	Severe constipation (obstructing tumour)	Bowel action more regular
8	Rectal bleeding	No bleeding
9	Discharge and bleeding	No improvement
10	Rectal bleeding	No improvement

and both patients died[7]. This report in conjunction with our experience prompts us to suggest that incomplete treatment of large cancers with PDT may be hazardous. Delayed haemorrhage may occur when the necrosed tumour sloughs, exposing a raw surface of malignant tissue with its fragile tumour vessels.

The purpose of using endoluminal ultrasound was twofold. first, to measure accurately the depth of the tumour prior to treatment and to avoid treating tumours that were large and could not be eradicated using PDT (the patient who bled had a stenotic tumour that could not be assessed by endoluminal ultrasound); and second to calculate the depth of necrosis produced from a standard photodynamic dose (photosensitizer dose × light dose), thus allowing dosimetric calculations and examination of current dosimetric theory[2]. If assumptions on tissue optical properties and photosensitizer concentrations are made from the available literature[12], the data presented in *Table 2* are consistent with current dosimetric theory[2].

In conclusion, PDT has promise for the treatment of small tumours of the gastrointestinal tract or for small residual areas of tumour after the bulk has been removed by other techniques (e.g. Nd YAG laser therapy, polypectomy or after limited surgical resection). A combination approach proved particularly effective in one of our patients. In its present form this technique should be used with caution for the treatment of advanced cancers, especially when other techniques such as Nd YAG laser therapy are effective.

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Gastrointestinal fistulas associated with large abdominal wall defects: experience with 43 patients

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Experience with 43 patients with gastrointestinal fistulas associated with a large abdominal wall defect is presented. The overall mortality rate was 60 per cent; 37 per cent in patients who underwent the primary procedure in the home unit and 74 per cent in those from elsewhere. An average of five operations per patient was performed. The abdominal wall defect developed spontaneously as a consequence of postoperative peritonitis in 24 patients (mortality rate, 71 per cent) and was created intentionally as a part of the 'open management' in 19 cases (mortality rate, 47 per cent). Errors in management were identified in 63 per cent of the patients and this adversely influenced the outcome. Patients with this condition should be referred early to tertiary care facilities where diversion of the intestinal leak away from the defect, prompt control of the associated intra-abdominal infection and adequate handling of the defect itself can be performed.

Keywords: Gastrointestinal fistulas, abdominal wall defect, intra-abdominal infection

Current mortality rates for patients with enterocutaneous fistulas range between 6 per cent and 20 per cent[1] Understanding the pathophysiology of this condition has resulted in a reduced mortality rate, from earlier figures of up to 62 per cent[2].

The wide range in outcome derives mainly from differences in the selection of cases and the referral pattern to individual institutions[1]. Sitges-Serra *et al.*[3] proposed a classification of postoperative enterocutaneous fistulas to achieve improved stratification of patients into more homogeneous groups. They divided patients into three groups: group 1, oesophageal, gastric, small bowel fistulas (low or high output); group 2, fistulas draining through a large abdominal wall defect; and group 3, appendiceal and colonic fistulas. The mortality rates in these groups were 18, 60 and 0 per cent, respectively. Fistulas in group 2, draining through a disrupted laparotomy wound, nearly always required operative treatment and were often fatal More recent series of external gastrointestinal fistulas[4–9] do not mention fistulas associated with a large abdominal wall defect as a separate clinical entity. Surgeons are increasingly confronted with intestinal leaks occurring in the depths of defects in the abdomen left open intentionally during 'open management' (or 'laparostomy') for severe intra-abdominal infection (IAI)[10–14] The clinical entity of gastrointestinal fistulas in association with large abdominal wall defects has not been previously discussed and we therefore present our experience with 43 such cases and discuss the aetiology, pathophysiology, management, prevention and prognosis of this condition.

Patients and methods

During the period from 1980 to 1988, 43 consecutive patients with postoperative, high output (>200 ml/day) gastroenteric fistulas of at least 20 cm^2 and draining through an anterior abdominal wall defect, were treated in one surgical unit Cervical and thoracic oesophageal, biliary, pancreatic and internal fistulas were excluded Patients with abdominal wall defects and fistulas draining via formed surgical drain tracts separate from the defect were also excluded. In 16 patients the initial operations were performed in the home unit and 27 patients were referred for management of complications following operations performed elsewhere

There were 24 male and 19 female patients with a mean age of 50 years (range 23–78 years) In 33 patients the fistulas originated from one site, in nine patients there was leakage from two sites, and in one patient the fistulas were situated in three sites (*Table 1*)

In 20 patients the fistulas originated from a surgical suture line; in 18 they occurred following incidental injury to the bowel during the primary operation or subsequent reoperations; and in five patients they arose from the bowel following procedures for infected pancreatic necrosis The primary procedures leading to the development of these complications are summarized in *Table 2*.

Management modalities

All patients were treated in the surgical intensive care unit. Wide-spectrum antibiotic therapy was used when indicated by clinical and laboratory findings All patients received total parenteral nutrition (TPN) via a central line Operative management in these patients evolved over the study period. Initially, the infected abdominal defect was treated by various methods such as direct application of gauze packs or Silastic® (Dow Corning, Reading, UK) foam with or without sump suction tubes. Operations were performed for clinical or radiological suspicion of IAI From 1984 such defects were treated by 'open management' using the 'sandwich technique'[15]. This allowed the collection and measurement of effluents before exteriorization of the fistula or proximal diversion.

From 1985 to date, all patients with postoperative, non-localized IAI were treated by an aggressive policy of planned, repeated laparotomies[16] The abdomen was closed whenever possible. In those patients with existing fistulas and infected large abdominal defects the open method was chosen, as abdominal closure was unsafe or impossible This policy entailed the exteriorization of all sources of leakage, if practical, and the placement of intestinal stomas away from the defect

Table 1 *Gastrointestinal fistulas through an abdominal wall defect Site and associated mortality rates*

Site	Number	Mortality
Oesophageal	1	1 (100)
Gastric	2	1 (50)
Gastroenterostomy	2	2 (100)
Pyloroduodenal	8	5 (63)
Small bowel	13	8 (62)
Large bowel	7	2 (29)
Multiple sites	10	7 (70)
Total	43	26 (60)

Values in parentheses are percentages

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Table 2 *Primary procedures leading to fistulas associated with abdominal wall defects*

Primary procedure	Number	Mortality
Gastroduodenal	17	13 (76)
Colorectal	12	5 (42)
Repair incisional hernia	1	0
Pancreatic necrosectomy	5	3 (60)
Adhesiolysis	4	2 (50)
Small bowel	2	1 (50)
Appendicectomy	1	1 (100)
Aortobifemoral bypass	1	1 (100)
Total	43	26 (60)

Values in parentheses are percentages

Results

Mortality

Twenty-six of the patients died (overall mortality rate of 60 per cent). Six of the 16 patients (37 per cent) undergoing surgery in the J. G. Strijdom Hospital died, while 20 out of 27 (74 per cent) of the referred patients died. Interestingly, the mean age of the patients who died was lower than the age of those who survived (46 *versus* 53).

Organ failure

Failure of one or more organ system as defined by others[17] occurred in 34 (79 per cent) of our patients with an associated mortality rate of 71 per cent.

Operations

These patients underwent 230 laparotomies (mean, five laparotomies per patient; range, 1–20). Seventy-five of the procedures were performed before the fistulas developed and 155 after The average number of operations in the patients who died and survived was 5·4 and 4·7, respectively.

Abdominal wall defects

In 24 patients these developed spontaneously and 17 died (71 per cent). In 19 patients the defect was created intentionally as part of our policy to avoid forceful, repeated closure of the oedematous abdominal wall in the presence of underlying IAI and ileus. Nine patients in this group died (47 per cent).

Errors in management

Careful analysis of each case revealed errors in management, either technical or of clinical judgement, in 27 (63 per cent) of the patients. The mortality rate in patients in whom such errors were or were not committed was 74 and 37 per cent, respectively. The common errors are represented in *Table 3*.

Hospital stay

The average hospital stay of the patients before transfer was 25 days; their mean stay at the J. G. Strijdom Hospital was 61 days. Mean hospital stay was 52 days in the patients who died and 73 days in those who survived.

Cause of death

In 20 cases (77 per cent), death was related to the fistula. In 12 of these it was due to organ failure caused by persistent IAI (seven of these patients were moribund on admission). In the other eight patients, death was caused by multiorgan failure but at death there was no evidence of residual or recurrent IAI In four of these the intestinal leak was not exteriorized because of technical difficulties, and in the other four, organ failure persisted despite complete diversion of intestinal contents away from the abdominal defect and the presence of a clean abdominal cavity. In six patients (23 per cent), death was caused by intra-abdominal or upper gastrointestinal haemorrhage (three patients), cardiorespiratory complications (two patients) and TPN-related metabolic complications (one patient).

Discussion

Large abdominal wall defects and intestinal fistulas usually occur in three clinical situations: severe postoperative peritonitis, loss of the abdominal wall, and as a complication of 'open management' Most commonly the problem arises as a consequence of reoperation for severe postoperative IAI Massive peritoneal contamination often results in 'obliterative peritonitis'[7], the early development of dense, vascular adhesions encasing the small bowel which becomes oedematous, adherent and friable, with acute and chronic inflammatory changes[18,19]. Repeated laparotomies aggravate the obliterative process and pose an increasing danger to the integrity of the bowel Repeated entries through the abdominal wall combined with closure under tension produce various degrees of abdominal wall oedema, necrosis and infection[20] The situation is complicated by raised intra-abdominal pressure owing to intestinal distension, fluid collections or mechanical ventilatory support. Intestinal juices from leaking suture lines or holes created in the fragile gut during re-explorations seep through the abdominal incision and digest the surrounding tissues. The abdominal wall eventually dehisces, resulting in the typical 'surgical disaster'. a patient with a large septic defect associated with a significant volume fistula

Acute full-thickness losses of the abdominal wall due to necrotizing infection, destructive trauma or *en bloc* tumour excision[21] lead to a similar result In those with electively instituted open management[10–14], there is usually a severe form of diffuse peritonitis and the abdominal defect is covered either with a gauze pack or a synthetic mesh. Fistulas occur as a result of exposure injury from gauze dressings[22], from dehiscence of pre-existing suture lines or from the trauma of frequent re-explorations. The mortality in these patients ranges from 31 per cent to 60 per cent in this series and those of others[3,12,21]. Levy *et al.*[23,24] presented a series of patients with intestinal fistulas in an eviscerated abdomen; they termed this entity 'exposed intestinal fistula'. The mortality rate in their 120 patients with postoperative peritonitis was 46 per cent. What is the cause for the high mortality rate in this condition? Errors in surgical technique or clinical judgement, both before and after the development of the condition, are common Bowel fistulas located in the depth of an infected abdominal wall defect have disastrous consequences[21]. This allows prolonged contact of large peritoneal surfaces with gastrointestinal contents, which increases the absorption of toxic products and perpetuates the septic state. The maceration and subsequent obliteration of all exposed structures make reoperation difficult and hazardous.

Table 3 *Errors in management before and after the development of intestinal fistulas associated with abdominal wall defect*

Errors	Number of patients
Early	
Late diagnosis of gastric leak following gastric stapling procedure for morbid obesity	2
Attempts to resuture intestinal leaks or failure to exteriorize	7
Repeated multiple reoperations without proper nutritional support	2
Failure to reoperate for IAI or delayed transferral	5
Technical or judgement errors at the time of the primary procedure	8
Late	
Delay in reoperation	1
Premature attempt to restore bowel continuity	1
Delay in exteriorization/diversion	2
Technical mistake during reoperation	1

The paucity of specific references to this entity in the literature is difficult to explain, but the increased popularity of a more aggressive management of postoperative peritonitis[25] may make these problems frequent[12,21,23,24].

Prolonged morbidity, limited financial resources and the high mortality rate make prevention of this condition of paramount importance. Faulty operative strategy and technical errors should be reduced, minimizing the incidence of postoperative peritonitis[26]. Bowel integrity must be preserved during intervention for IAI

Surgical treatment requires three considerations· the fistula, the IAI and the abdominal wall defect. Diversion of intestinal effluents away from the defect is mandatory[20,21] Goligher[27] emphasized the importance of exteriorization of the ends of leaking or fistulated small bowel. Others applied this method for compromised bowel involved in the process of obliterative peritonitis[18] or in various intra-abdominal infectious and obstructive conditions[28] This can be difficult, however, when the bowel is oedematous and distended and the mesentery thickened. A disadvantage of this approach is the frequent injury and consequent sacrifice of adjacent intestinal segments. An alternative is to bring out a proximal diverting jejunostomy fashioned in an uninvolved segment of the bowel. Contrary to some views[27,28], such proximal jejunal vents are well tolerated[18]; two of the patients in this series had end-jejunostomies created just beyond the duodenojejunal flexure and a weight gain was achieved in the 6 months preceding the closure of their stoma.

Exteriorization or diversion is not possible in leaks from fixed bowel segments such as the duodenum; alternative methods are required, usually with less satisfactory results. Mughal *et al.*[12] exteriorized only solitary fistulas and suggested that leaving multiple fistulas undisturbed at the base of the defect was safer than excising an anatomically undefined mass of bowel. The distance of the fistulous opening in the bowel from the surface of the defect and the condition of the peritoneal cavity has bearing on the necessity for diversion. Exposed fistulas near the surface where the underlying peritoneal cavity is clean and sealed away from the intestinal contents do not need immediate diversion[23,24].

The results of this study do not demonstrate better results with more aggressive surgical policies for IAI It is possible, however, that in some patients such an approach was used too late The experience with four patients is characteristic. All were referred with an established fistula and an abdominal wall defect. Their fistulas were diverted away from, the defect, their abdomens were managed with the 'open method' and staged, planned relaparotomies were performed All four died from multiple organ failure in spite of the macroscopic eradication of sepsis. This illustrates the limits of the mechanical–anatomical approach in patients whose defence mechanisms have fallen below a critical level.

What is the correct management of the septic abdominal wall defect? Forceful closure of the abdominal wall in these circumstances is associated with a high mortality[21]. The use of pedicled flaps to cover the infected defect in such compromised patients carries an unacceptably high rate of wound complications[21] The condition forces the surgeon to adopt the method of laparostomy. Lessons learned in the elective 'open management' of severe IAI can be applied to the dehiscence of the septic postoperative abdomen We, and others[10,15,16,21,29], prefer to cover the defect with a synthetic mesh to protect the exposed viscera from further injury. In the absence of a proximal vent, openings in the exposed bowel can be exteriorized through the mesh and effluents collected by means of suction tubes When the IAI subsides and relaparotomies are no longer foreseen, the mesh is removed and skin cover is achieved by the combination of split-skin grafting and wound contracture Further restoration of the abdominal wall structure to improve function and cosmesis occurs after the closure of all stomas and the complete recovery of the patient Levy *et al.*[20,30], however, proposed immediate closure of the septic defect using medial myocutaneous rectus abdominis advancement flaps. They claim improved results when the primary closure was combined with defunctioning of the fistula, thorough peritoneal debridement and capillary drainage.

The present study suffers from many pitfalls found in the literature on severe IAI; it is retrospective and includes a small sample of patients with multifaceted aspects of aetiology and treatment. Since 1986 we have attempted to improve the stratification of our patients by using the APACHE II scoring system[31], but have found it somewhat unhelpful in patients requiring multiple laparotomies. We can, however, conclude that the combination of a large abdominal wall defect and gastrointestinal fistulas usually represents an advanced and neglected case of postoperative IAI. Errors in management are a common aggravating factor. To reduce morbidity and mortality rates, patients with this condition should be referred earlier to tertiary care facilities where diversion of the intestinal leak away from the defect, prompt control of the associated IAI and adequate handling of the defect itself can be performed

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Case report

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Traumatic love bites

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While tactile and intimacy techniques were described in the early part of the first millenium[1], it was Hultgen in 1910 who drew attention to human bites in the medical literature[2]. However, as a pathological entity, it was described first in 1930[3] By 1942, about 790 cases were reviewed[4]; the violence was considered both as a means of defence[5] and as a method of attack[6] Barnes and Bibby in a study of 341 human bites stated that bites arising from sexual practices were not uncommon[7]. In 1950 a large series of human bites of the head and neck was reported (46 cases) but with no mention of love bites[8]. Curtin and Greely illustrated an avulsion in the tip of the tongue and a laceration of the lower lip in two negroes bitten passionately by their girlfriends[9]. The first clear description was reported in 1979 by Tomasetti *et al.* in a study of 25 cases of human bites of the face, of which five were due to passion[10].

Seven instances of love bites are presented. The study highlights the varieties of human bites with specific reference to traumatic love biting.

Case reports

Case 1

A 35-year-old man presented with a right supraclavicular, hard, non-tender mobile mass, 2 cm in diameter and with a central hole He became aware of it 3 months before admission A provisional diagnosis of epidermoid cyst was made. The mass was excised under general anaesthesia and on bisection the centre harboured a broken plastic tooth. Retrospective enquiry revealed that he had attended a Halloween party one year before when he was bitten by a lady dressed as a vampire; they were both drunk on love making.

Case 2

A 38-year-old man presented with a right cervical abscess, 10 cm in diameter with surrounding cellulitis. The abscess was incised and drained and the pus grew *Staphylococcus epidermidis* and *Bacteroides* species In view of such unusual bacterial skin flora, a more detailed history was taken. He admitted a violent love biting 3 weeks before his operation

Case 3

An 18-year-old male presented with a bleeding neck following a love bite 2 h before admission. The bleeding was trivial but associated with deep bite marks traumatizing the external jugular vein. This was treated by thorough cleansing and application of a pressure dressing The bleeding ceased and he was well when reviewed 7 days later

Case 4

A 26-year-old woman presented with right neck cellulitis (5 cm in diameter) of 3 days duration. After a careful enquiry, she admitted a ferocious love biting by her new boyfriend She was treated on an outpatient basis with oral metronidazole and flucloxacillin together with tetanus prophylaxis, giving a satisfactory result when reviewed 7 days later

Case 5

A 28-year-old man presented with a right neck cellulitis of 2 days duration He was embarrassed to admit love biting by his frustrated girlfriend after he returned from a long trip abroad. He was treated as in Case 4

Case 6

A 23-year-old woman presented with a bleeding areola and complete avulsion of her left nipple following a savage love biting by her drunk 26-year-old husband. They were newly married and on their honeymoon. She underwent a surgical reconstruction of the remaining areola.

Case 7

A shy 19-year-old woman presented with a left breast abscess (5 cm in diameter in the upper medial quadrant) After a careful interview, she admitted love biting by her short statured boyfriend. Incision and drainage was performed with a good result. The pus grew *Staphylococcus aureus.*

Discussion

Reported cases of complicated human love bites represent the tip of the iceberg, partly because of the embarrassment of the patient about seeking medical advice and partly because of the reluctance of the physician to report such cases. Love bites represent only a part of the spectrum of the human bite while clinical vampirism and cannibalism constitute the violent extreme.

The virulent nature of human biting stems from the fact that the oral cavity harbours a wide range of bacterial flora with α-haemolytic *Streptococci* and *Bacteroides* species being the most frequent isolates[5]. While dog bites are practically clean and the wound heals with no secondary infection, human bites are potentially infective and serious[11]. Indeed, death has been reported due to septicaemia after a pyogenic arthritis caused by a clenched fist injury[12]. Antibiotic cover should be routinely administered in all human bite wounds[5,9,10]. Tetanus prophylaxis is important; the assertion that tetanus cannot be

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transferred by human bites is untenable[5,6,10]. The cervical mass and the bleeding neck represent pseudo-vampirism rather than real vampirism, i.e. the bleeding inflicted during biting was accidental and not intentional. Clinical vampirism has been reported in patients with personality disorders such as schizophrenics and sadists whilst committing a sexual or aggressive act (with or without blood sucking) on a dead or dying person[13]. This is in contrast to mythical vampirism in which the dead feed on the living[14]. However, in the French literature, a strange masochistic phenomenon of auto-vampirism has been reported. Two cases were reported. One patient used to cut his neck veins with a knife whilst in front of a mirror, tilting his head, allowing the blood to trickle on to his cheek and sucking it. Another patient in the hospital used to enjoy pulling out her venous line repeatedly, watching the blood flowing freely and sucking it[14].

Biting with blood sucking (vampirism) is one of the most gruesome superstitions in the world; it originates from a Slavonic folklore. The nocturnal demon leaves its grave to prey upon the living victims. Thereafter, it must return to its grave before dawn. Victims after death become vampires[15]. The word, vampirism, is derived from the Vampire, a blood sucking bat of *Microchiroptera* species in the Neotropics; it is a very shy animal that scans the skin of the prey with the aid of its modified nose acting as a heat sensor to the best blood engorged area. It feeds on the blood by puncturing the skin with its modified front teeth and lapping the blood which oozes forth. Skin wounds are generally clean and free of complications.

Biting and eating human flesh (cannibalism) represents an arrest of human development at sado-oral stage according to psychoanalytic theory[13]. Anthropologically, this primitive phenomenon has been reported in cannibalistic tribes in New Guinea, West Africa, South America and the West Indies. It was also reported in schizophrenic patients. Cannibalism is associated with a fatal slow viral transmissible disease of the brain (kuru)[16].

Human love bites have received scant attention in the medical literature. The traditionally called 'love bite' is a misnomer, since it represents a gentle nibbling preparatory to orgasmic climax without skin breach, caused by inhibitory cortical control over the limbic system (see below). Consequently, it is considered to be a benign form of biting with no complications. Occasionally love bruises may follow strong continuous suction kisses (rather than actual biting). It is preferable to use the term 'pre-coital love bite' to differentiate it from a 'coital love bite'. The latter represents a breach of epithelial continuity caused by an involuntary jaw spasm initiated during the orgasmic climax and maintained throughout the period of sexual act as a part of the general excitatory repertoire and limbic system stimulation. Coital love bite may lead to an uncontrollable penetrative avulsive trauma in the head and neck of a bitten partner who cannot recognize such trauma because of the modified pain threshold (high) owing to sexual enjoyment. The faciocervical predilection is explicable on the basis of being the only accessible area for biting when the two partners are cocooned *en copula*. The facial predilection is well illustrated in the study by Tomasetti *et al.* (three involving the lower lip, one involving the tongue and one the ear and eyelid)[10]. In this series, all but two bites affect the neck region. Breast abscess and nipple avulsion were probably caused by the discrepancy in the heights of the partners (with the male being shorter than the female).

Coital love bites (as opposed to pre-coital ones) can lead to a serious trauma because of various factors, namely the broad spectrum of oral bacterial flora, the deep penetration caused by an uncontrollable jaw spasm, tissue necrosis secondary to mechanically compromised tissue perfusion and blood supply caused by incisor teeth, the delay in treatment because of embarrassment, and finally, its faciocervical predilection. Such cases must be treated promptly and properly; admission may be considered when surgical intervention is deemed necessary.

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Triad of anorectal stenosis, sacral anomaly and presacral mass: a remediable cause of severe constipation

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Two neonates with intestinal obstruction and two children (aged 1 and 4 years) with severe constipation since birth are reported in whom stenosis of the distal rectum was found. In association with the rectal anomaly, three of them had a presacral tumour (teratoma in two, hamartoma in one) and all had a deformed sacrum. An embryological hypothesis to explain this association has been postulated by Currarino, after whom this triad has been named. Two patients were related (father and daughter). The role of hereditary factors in the occurrence of the syndrome has been reported before. Operative treatment of the rectal stenosis was necessary in all patients. Preoperative diverting colostomy was performed in three cases, followed by a posterior sagittal approach to excise the rectal stenosis and the presacral mass. In one case, persistent cerebrospinal fluid leakage required re-exploration for closure of a tear in a congenitally abnormal dural sac. The fourth patient had undergone a low anterior resection in the past via the abdominal route and needed rectal dilatation afterwards for some time. The final result in all patients appears satisfactory, although follow-up is short. Most cases of this triad have been reported in children but a number of patients have been diagnosed only as adults. Recognition of this triad should imply a careful search for neural crest malformations. Operative treatment to correct all soft tissue anomalies leads to good results.

Keywords: Rectum, presacral tumour, teratoma, sacral meningocele, split notochord syndrome

Constipation has no detectable organic cause in the great majority of patients. Another category of patients suffers from Hirschsprung's disease, colorectal neoplasms and neurological disorders. Occasionally, a rare anatomical malformation may underlie severe constipation. Recently we treated three children with stenosis of the anorectum associated with a presacral tumour and sacral bony deformity. This association of anomalies is also known as Currarino's triad[1]. Furthermore, we found that the father of one of the patients had been treated as a child for a similar anomaly but that the true nature had not been recognized at the time. This association of anomalies can be encountered in children and adults but appears to be relatively unknown. We therefore report our experience.

Patients and methods

Patient 1

A boy, born in 1987 at term after a normal pregnancy, developed intestinal obstruction on the second day of life. Near total stenosis of the distal rectum was found on examination. Hirschsprung's disease was excluded by rectal biopsies. On the plain radiograph, partial sacral agenesis was seen. After a right transverse colostomy he thrived. At the age of 9 months magnetic resonance imaging of the pelvis demonstrated a presacral tumour (*Figure 1*). Exploration through a posterior sagittal approach revealed a grey-white mass extending into the completely obliterated rectum. The mass was excised and part of the distal rectum was resected. The continuity of the rectum was restored by an end-to-end anastomosis. Histological examination showed a mature (benign) teratoma. After closure of the colostomy constipation recurred but was easily managed with diet and mild laxatives. He is now 2 years old and is developing normally.

Patient 2

A girl had had severe constipation since birth in 1987. Examination at the age of 1 year revealed a tight stenosis of the distal rectum. Rectal biopsies and anal manometry showed no evidence of Hirschsprung's disease. Radiographs of the sacrum showed a malformation with a central defect. Ultrasonography of the presacral area failed to demonstrate a mass. A right transverse colostomy was performed to decompress the massively dilated colon. Subsequent exploration via the posterior sagittal approach revealed an encapsulated tumour with a diameter of 3 cm in the presacral space with an extension to the sacrum. The tumour was not connected with the rectum and was excised completely. In the rectum a circular stenosis 5 mm in length was found. The stenosis was partially excised and the resulting defect was closed transversely to increase the diameter of the rectum. Histological examination, both of the tumour and the stenosis, showed a mature

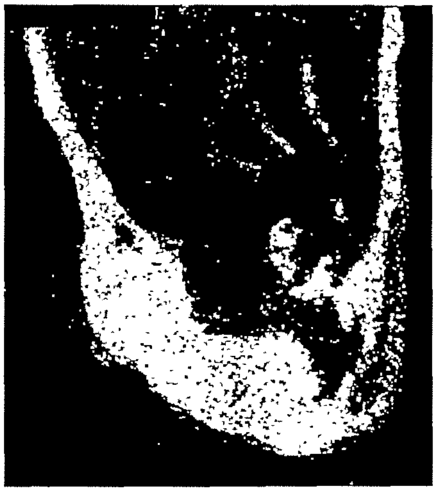

Figure 1 *Magnetic resonance image of patient 1 showing a presacral mass which extends into the rectum*

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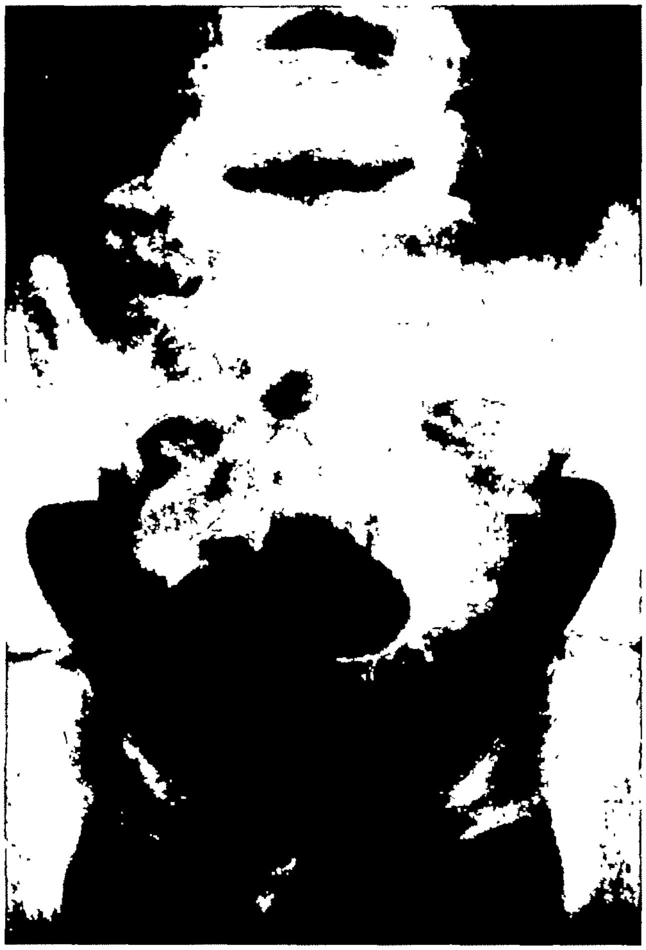

Figure 2 *Plain radiograph of the bony pelvis of patient 3 showing an asymmetrical deformity of the sacrum with a central defect*

teratoma The postoperative course was complicated by leakage of cerebrospinal fluid Re-exploration showed this to be caused by a tear in an anomalous extension of the dural sac, that was closed successfully. After closure of the colostomy, mild constipation is managed with oral laxatives.

Patient 3

This girl had had severe constipation since birth in 1983. Rectal examination at the age of 4 years revealed tight stenosis of the distal rectum Hirschsprung's disease was excluded by rectal biopsies A plain radiograph of the pelvis showed a partial agenesis of the sacrum (*Figure 2*). A right transverse colostomy was performed Subsequent exploration by the posterior sagittal approach revealed a presacral tumour that extended into the rectal wall. The mass and distal rectum were excised and end-to-end anastomosis of the rectum was performed Histological examination showed a hamartoma. After closure of the colostomy the pattern of defaecation was normal

Patient 4

This patient is the father of patient 3 At the age of 10 days he underwent laparotomy for suspected intestinal obstruction but only a stenosis of the rectum was found and dilated Subsequently, constipation occurred and a tentative diagnosis of Hirschsprung's disease was made Low anterior resection of the distal rectum was performed at the age of 4 years Histological examination did not convincingly support the diagnosis of Hirschsprung's disease After operation he developed rectal stenosis for which repeated dilatations were performed while he remained on laxatives Gradually over the years the pattern of defaecation improved and he no longer requires laxatives. Radiographs of the sacrum showed a similar deformity to that seen in the other patients

Discussion

The association of rectal stenosis, presacral mass and sacral deformity was described by Currarino *et al.* in 1981[1]. The presacral mass may be a teratoma, anterior sacral meningocele or an enteric cyst. Earlier, Ashcraft and Holder had reported a similar syndrome and emphasized the hereditary aspects[2]. The diagnosis may be delayed until adulthood[3–5].

Detailed reports have been published on the association of anterior sacral meningocele and bony sacral deformity, both in children and in adults[6–10]. Many of these patients also had constipation. Although several of them appear to have anorectal malformations, most authors consider that the constipation was caused by external compression of the rectum by the presacral meningocele. Others have reported the finding of presacral teratoma in association with anorectal stenosis[2–4,11,12].

With regard to embryogenesis, Currarino *et al.* postulated[1,13] that before the 20th day a close relation exists between endoderm (future intestinal tract) and ectoderm (future spinal column). Mesodermal tissue then forms laterally and fuses in the midline around the notochord to form the vertebral column, thus separating endoderm and ectoderm. Failure of this mesodermal fusion, either due to adhesions or to anomalies of the notochord, results in persisting connections between intestinal tract and spinal column in the form of a fistula, meningocele, enteral cyst or teratoma This is called 'the split notochord syndrome' and can occur at thoracic, lumbar or sacral level[14–16].

The exact nature of the rectal stenosis has received relatively little attention in the literature. As stated, some authors consider extrinsic compression either by the presacral mass or by adhesions to be the cause of the stenosis. Others have reported extension of the teratoma into the rectal wall[2,3,11] In three of our patients the nature of the rectal stenosis could be defined Unfortunately we could not identify what the exact nature of the rectal stenosis had been in patient 4. In all three cases a tumour was found in the rectal wall, a teratoma in two and a hamartoma in one. In two patients the presacral tumour extended into the rectal wall In one the rectal teratoma was not connected to the presacral tumour, but had the same histology. We therefore feel that it is not likely that the rectal stenosis is caused by extrinsic compression or perirectal adhesions, but consider that the tumour in the rectal wall is the most plausible explanation

The management of these patients begins with establishing the true nature of the disease. Rectal examination of all patients with severe constipation is mandatory to detect rectal stenosis, which is always located distally in this syndrome. Radiographic examination of the bony pelvis in these patients may reveal sacral defects. In these cases, thorough investigation is indicated to detect a presacral mass, particularly an anterior meningocele. Although ultrasonography did not detect a 3 cm presacral mass in one of our patients, we think that it can be of use in these cases to detect a space occupying lesion If a meningocele is found, neurosurgical exploration should precede intestinal surgery. Additional computed tomographic scanning or magnetic resonance imaging is indicated to detect anomalies of the spinal canal. The need to excise a presacral teratoma is based on two considerations: first, that malignant presacral teratomas have been reported[3,5]; second, the presence of teratoma inside the rectal wall in a number of patients. In patient 2 the rectal stenosis was not connected to the presacral mass and therefore was not excised completely. The histological report of a teratoma was unexpected. Since it was a mature teratoma and malignant transformation of a benign teratoma has never been proved, it was decided to follow this patient carefully by rectal examination and serum α-fetoprotein determinations.

Because of the presence of tumour in the rectal wall in most cases, conservative treatment with laxatives or repeated dilatation will not lead to satisfactory results. The long-term outcome of excisional surgery with regard to rectal function has been reported to be good[2,3,7] Most of these patients have not been operated on by the posterior sagittal approach. Follow-up in our patients has been too short to evaluate the long-term results of this approach in these cases. In most severe rectal stenosis, diverting colostomy will be indicated because of massive faecal stagnation.

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Case report

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Case of simultaneous diverticulosis, lipomatosis and volvulus of the small intestine

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Two cases of diverticulosis and lipomatosis of the small intestine have been reported[1,2]. One of these cases had a small bowel volvulus. We report a further case that includes a volvulus.

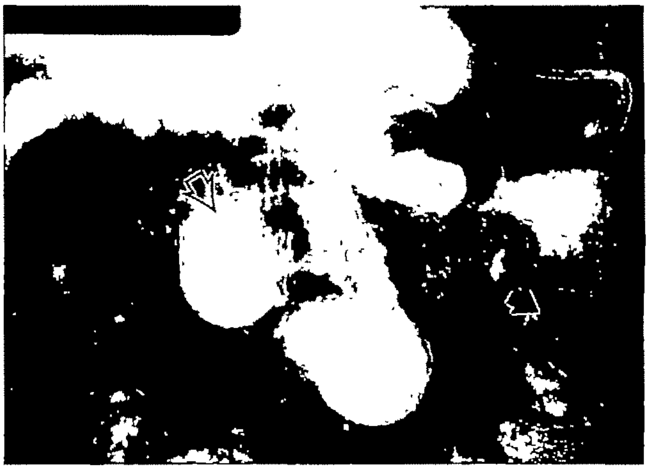

Figure 1 *Small bowel enema film. The clear arrow illustrates a large diverticulum and the black arrow an intraluminal polyp*

Case report

A 56-year-old man presented with a 4-month history of bouts of postprandial epigastric pain, with intermittent swelling in the right hypochondrium. Pain occurred on eating, he had lost 10 kg in weight. On examination, he was tender in the epigastrium and right hypochondrium.

An abdominal ultrasound was normal. Gastroscopy revealed a small area of non-specific superficial gastritis, the barium enema was normal, as was colonoscopy. A small bowel enema showed multiple diverticula and intraluminal polyps throughout the jejunum and ileum (*Figure 1*). At laparotomy, there was a 360° clockwise volvulus of the small bowel, without evidence of vascular compromise. After derotation a length of abnormal small bowel was noted. It began 50 cm from the duodenojejunal flexure and extended to 90 cm from the ileocaecal valve. It was thickened and dilated throughout its length. There were numerous large diverticula, up to 7 cm in diameter, on both the mesenteric and antimesenteric borders. Multiple polyps could be palpated in this segment, one of which was producing an intussusception. The whole of the affected segment was resected and end-to-end anastomosis was performed. He made an uneventful postoperative recovery.

At histological examination multiple discrete submucosal lipomata were found, some at the base of a diverticulum.

Discussion

The occurrence of the diverticulosis and lipomatosis together could occur by chance. The incidence of small bowel diverticulosis is generally reported as being between 1 and 1·5 per cent. Benign small bowel tumours are relatively rare, although lipomata are one of the more common types[3]. However, the lipomata may have caused an intermittent or incomplete obstruction encouraging the development of pulsion diverticula. The lipomata may also have weakened the bowel wall, as shown by the attenuation of the muscle layer over them and the fact that many lipomata and diverticula occurred together. Krishnamurthy *et al.*[4] examined the histology of seven cases of small bowel diverticula and found an abnormality of the musculature or a neuropathy in each. This was felt to predispose to the build up of abnormal intraluminal pressures. No such abnormalities were demonstrated in our case, making the lipomata the most likely cause.

Volvulus is a recognized complication of small bowel diverticulosis[5]. The abnormal weight distribution of the bowel may be a factor in its occurrence. We suggest that diverticulosis, lipomatosis and small bowel volvulus are linked, with lipomatosis being causative in the development.

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Case report

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Cavernous haemangioma of the oesophagus

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Bleeding from benign gastrointestinal tumours accounts for only 0·6 per cent of cases of haematemesis[1]. Cavernous haemangiomas of the gastrointestinal tract are rare, their incidence being lower than that of adenomas, fibromas and leiomyomas[2]. The oesophagus is the least common site of vascular tumours in the entire gastrointestinal tract A case of one of these exceptionally unusual tumours is described, together with the findings on magnetic resonance imaging.

Case report

A 49-year-old man presented with a 12 h history of haematemesis, preceded by 1 week of intermittent retching. There was no abdominal pain or melaena He had suffered many other, more minor, episodes of bleeding over the preceding 6 years but had never sought medical advice. There was no previous dysphagia He took no drugs or alcohol During examination he vomited 300 ml of bright red blood, but otherwise no physical abnormality was demonstrated Initial haemoglobin concentration was 13·7 g/100 ml and this did not fall in the subsequent 72 h

Oesophagogastroduodenoscopy showed a 4 cm diameter submucosal tumour protruding into the lumen of the distal oesophagus (36–40 cm). The mass was readily indentable, suggesting vascularity, and therefore biopsy was deferred. Magnetic resonance imaging obtained on a 0·5 T superconducting magnet defined the anatomical relationships of the mass and the oesophagus (*Figure 1*) These scans show a well-defined high signal area confined to the oesophageal wall There were no flow voids or evidence of enlarged feeding vessels

Subsequently the patient suffered a second episode of haematemesis, during which the haemoglobin level fell by 3·0 g/100 ml in 24 h. Repeat endoscopic examination demonstrated a linear ulcer overlying the tumour mass and a visible bleeding vessel within it In order to stop the episodic bleeding, the tumour was excised The oesophagus was approached via a left thoracotomy and the distal 5 cm were resected to include the gastro-oesophageal junction. The oesophagus was reimplanted into the stomach No drainage procedure was used The patient made a satisfactory recovery

Macroscopic examination of the operative specimen confirmed the endoscopic appearance of a 4 cm tumour nodule with a normal mucosal covering, apart from a central focus of ulceration Histological examination showed it to consist of numerous vascular channels of varying size. These channels were predominantly thin walled with a ring of flattened cells which stained positively with Factor VIII Although the muscularis was hyperplastic there was no evidence of a leiomyoma. The appearances were benign and those of a cavernous haemangioma

Discussion

Although haemangiomas may affect any organ or tissue, they are most commonly associated with the skin A review of benign vascular lesions of the gastrointestinal tract describes the pathological variants encountered in 106 cases discovered in 1 400 000 patient records[2] Single polypoid cavernous haemangioma represented 18 per cent of these cases at a time when the frequency of angiodysplasia of the colon was underestimated. The oesophagus was the least common site. In a combined series of 13 460 autopsies only three oesophageal haemangiomas were reported[3,4].

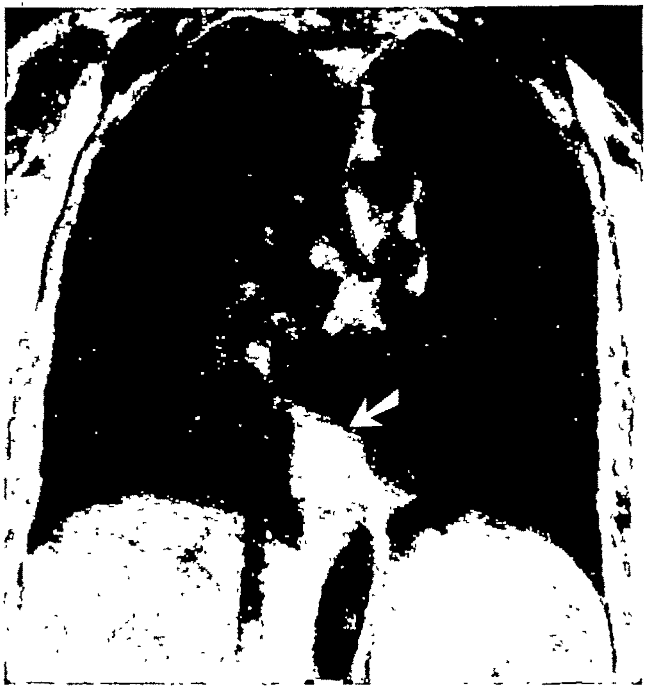

Figure 1 *Coronal magnetic resonance image of the thorax showing the haemangioma (arrowed)*

Despite their vascularity, oesophageal haemangiomas usually present with dysphagia or retrosternal discomfort; haematemesis is extremely rare The age at presentation is very variable (4 months–70 years) and the sex incidence is equal.

In theory, the pattern of signal response found on magnetic resonance imaging may help to differentiate haemangiomas from other tumours. However, although serpiginous patterns have been described in soft tissue haemangiomas, they were not present in this case[5]. Furthermore, a uniform increase in signal on certain scans may occur not only in haemangiomas (as in this case) but also in some metastases. Therefore, magnetic resonance imaging, while demonstrating the anatomical relationships of the tumour, did not help in the diagnosis of haemangioma

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Short note

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Closure of subcutaneous fat: a prospective randomized trial

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It has been a traditional surgical practice to obliterate dead space This rule has been applied in particular to subcutaneous tissues, especially where fat is plentiful.

Using cholecystectomy as a model, a prospective randomized clinical trial was conducted to determine the value, if any, of suturing subcutaneous fat.

Patients and methods

A total of 200 patients undergoing cholecystectomy was admitted to the trial and randomized by sealed envelopes into two groups. Randomization was stratified for sex and restricted to give equal numbers of men and women in each group

Three consultant surgeons participated using a similar technique. Patients gave informed consent to participation; they were all undergoing cholecystectomy for chronic cholecystitis. Patients with chronic obstructive airway disease and those requiring choledochotomy were excluded Both groups had standard premedication and anaesthetic. Kocher's incision was used in all patients

In group 1, closure of abdominal incision was done by continuous suturing of peritoneum and posterior rectus sheath as one layer using Number 1 coated polyglactin 910 (Vicryl®, Ethicon Ltd., Edinburgh, UK) on a tapercut 40 mm needle. The anterior rectus sheath was similarly sutured The subcutaneous fat was approximated using interrupted Number 2 coated polyglactin 910 (Vicryl) sutures approximately 1 cm apart. The time taken for suturing subcutaneous tissues was noted. The skin was approximated by Proximate autostapler (Ethicon Ltd., Edinburgh, UK) applied 8 mm apart.

In group 2, a similar technique for wound closure was used except that the subcutaneous tissues were left unsutured

The wounds in both groups were dressed with a single Dermicel adhesive dressing (Johnson and Johnson Ltd., Slough, UK). These were removed after 24 h. The area of serosanguinous soiling on dressings was measured in square centimetres by placing a transparent polythene sheet with markings in square centimetres on top of the soiled steripad Area of soiling greater than 3 cm^2 was considered significant.

The thickness of subcutaneous fat was measured in both groups. After the operation the wound was examined daily for the development of seroma, haematoma, wound infection and wound dehiscence until the patient was discharged from the ward

Results

Overall, there was no significant statistical difference in complications between the two groups (*Table 1*) The dressings were significantly soiled by serosanguinous discharge in group 2 patients as compared with group 1 patients ($P<0\cdot04$, χ^2 test). The mean thickness of subcutaneous fat in group 1 patients was 2·5 cm (range 0·8–5 cm) and in group 2 patients was 2·4 cm (range 0·7–4·8 cm). It took 4 min (mean) to suture subcutaneous tissue in group 1 patients (range 2·5–8 min).

Table 1 *Results of the suturing (group 1) or not suturing of the subcutaneous fat (group 2)*

	Group 1	Group 2	Significance
Number of patients	100	100	
Male : female ratio	15:85	15:85	
Mean age (years)	37 (2·6)	36 (2·7)	n s.*
Significant soiling of dressing	8	37	$P<0\cdot04$†
Postoperative seroma	0	1	n s.†
Postoperative haematoma	2	1	n s.†
Postoperative wound infection	4	3	n s †
Mean postoperative hospital stay (days)	7 (0·3)	6 (0·3)	n s *

Values in parentheses are s.e m ; n.s , not significant, * Student's t test, † χ^2 test with Yates' continuity correction, 1 degree of freedom

Discussion

Technical details of wound closure are important; whereas skin closure is extensively researched[1–4], approximation of subcutaneous tissues by absorbable suture material appears to have been taken for granted as correct. Standard teaching stresses avoidance of dead space during wound closure[5,6].

It took, on average, 4 min extra to complete oprations in group 1 patients. Significant soiling of dressings in group 2 as compared with group 1 suggests that wound seepage is reduced after closure of fat, or alternatively it may mean either a true decrease in serosanguinous discharge or trapping of the discharge, preventing soiling of the dressing. If the discharge is truly decreased then the possibility of a collection in the wound would correspondingly decrease; on the other hand, wound seepage may be desirable in as much as it prevents formation of a seroma or haematoma and subsequent infection. This study shows that there was no significant difference in complications between the two groups. Although only closure of Kocher's incision was tested, it is reasonable to extrapolate these results to other abdominal incisions.

It is concluded that suturing subcutaneous fat in the upper abdomen reduces wound seepage and may cut the requirement for postoperative dressings.

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Case report

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Early pregnancy masquerading as a marker for malignancy in a young woman with curable neoplasm of the pancreas

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The so-called solid or cystic papillary neoplasm of the pancreas is a rare type of tumour occurring almost exclusively in young women. This neoplasm is not associated with any endocrine dysfunction, and typically it has assumed considerable size when discovered. Since most cases are curable by surgery, their distinction from other types of neoplasms with less favourable prognosis is important[1]. The case reported here illustrates a potential pitfall in this context.

Case report

A 19-year-old previously healthy woman was admitted to hospital because of intermittent abdominal pain of 2 weeks duration. A pregnancy test was positive and she was examined by ultrasound with regard to ectopic pregnancy. The uterus had normal size and uniform echo distribution, but in the right upper quadrant of the abdomen an 8 cm non-homogeneous partially cystic mass was demonstrated. Considering the history given, this lesion was suspected to represent an ectopic pregnancy. At subsequent exploratory laparotomy the mass was found to be located within the head of the pancreas. A biopsy was taken and pathological examination revealed an islet-cell neoplasm. The pelvic organs looked quite normal, and the elevated serum chorionic gonadotrophin (HCG) level was now interpreted as an expression of malignancy although no metastases were evident. Tumour resection was not attempted, but the patient was referred to the University of Michigan Medical Center for further evaluation and treatment. Repeat serum analyses showed levels of β-HCG at 775 milliunits/ml (normal <10 milliunits/ml) and α-HCG at 4 ng/ml (normal <1.2 ng/ml). Angiographically the tumour appeared hypervascular with the exception of supposedly necrotic central areas.

There was no apparent invasion of the surrounding major vessels, and neither angiography nor computed tomography (*Figure 1*) showed any evidence of liver metastases. The patient was reoperated on and the tumour was found to be removable by a Whipple procedure. The HCG values did not fall after the operation as expected but continued to rise, and a week later (3 weeks after initial admission) repeat ultrasound examination revealed an intrauterine pregnancy with measures that suggested an age of approximately 7 weeks. Histological examination of the resected tumour did not verify the previous diagnosis of islet-cell carcinoma, but showed a picture characteristic of the so-called solid or cystic papillary neoplasm of the pancreas (*Figures 2* and *3*). The patient, who subsequently underwent abortion, is doing well 1 year after the operation without any evidence of tumour recurrence.

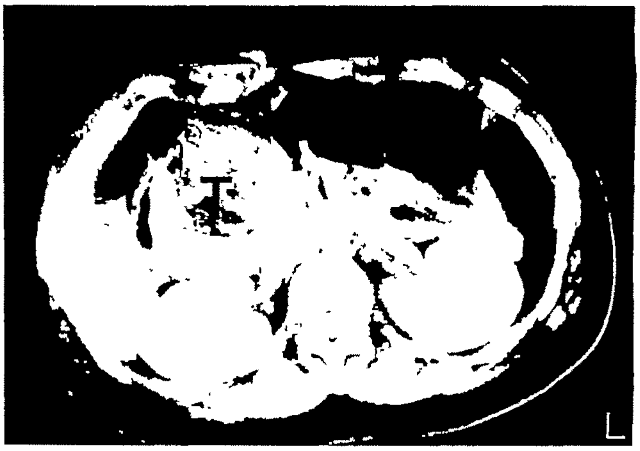

Figure 1 *Complete tomography scan showing the large solid or cystic papillary tumor (T) in the head of the pancreas*

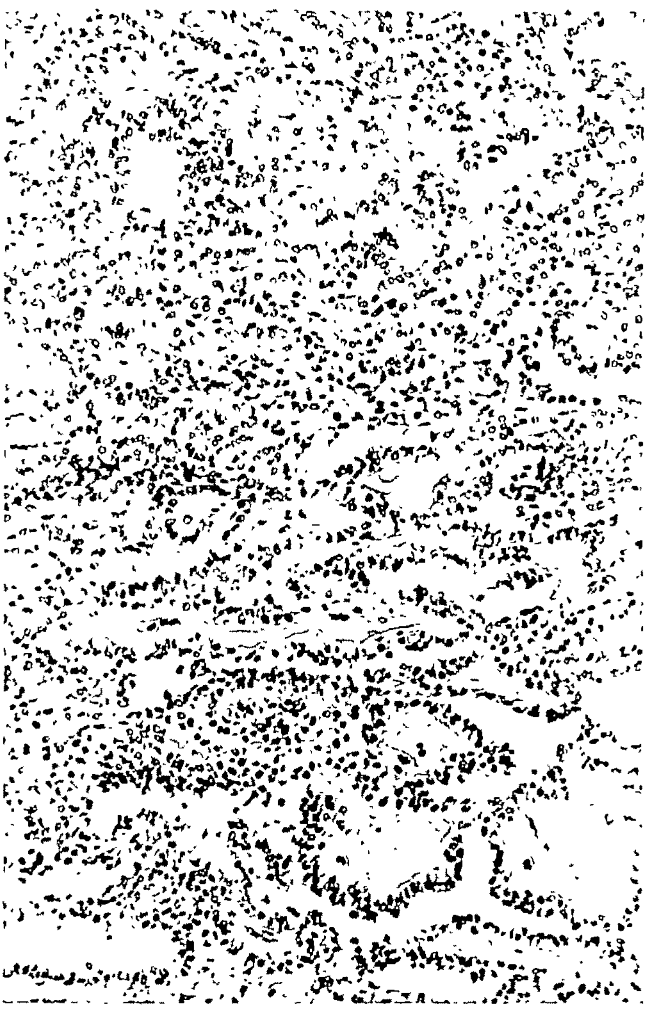

Figure 2 *Histological section demonstrating an area of characteristic papillary growth pattern in the so-called solid or cystic papillary neoplasm of the pancreas (hematoxylin and eosin stain, × 125)*

Discussion

Studies of patients with endocrine pancreatic neoplasms have indicated that serum levels of HCG and its subunits are specific markers for malignancy[2,3]. Likewise, immunocytochemical demonstration of α-HCG has been found to be associated with malignant behaviour in a large series of islet-cell tumours[4]. Thus, early and unexpected pregnancy is an apparent pitfall in the clinical setting presented here where a pancreatic tumour was discovered in a young woman.

Although endocrine tumours of the pancreas are usually small lesions (unlike the so-called solid or cystic papillary

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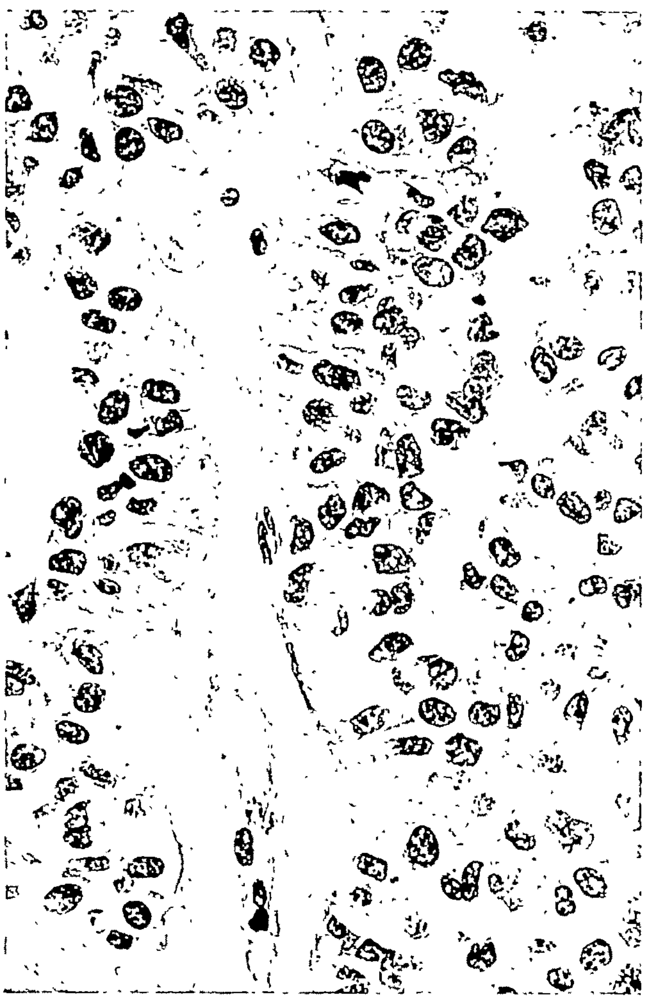

Figure 3 *Detail of papillary growth showing characteristic cellular features with apical, often grooved, nuclei that have finely dispersed chromatin and inconspicuous nucleoli (hematoxylin and eosin stain, × 500)*

neoplasm described here), tumour size is of no differential diagnostic value since islet-cell tumours can occasionally assume huge proportions and become partially cystic from degeneration[5]. The microscopic features of the entities under discussion show similarities but do have distinctive characteristics that allow definite diagnosis by aspiration cytology[6]. An important advantage of aspiration cytology as opposed to radiological examinations in the present context is that it does not harm an early pregnancy.

The fact that most solid or cystic papillary neoplasms of the pancreas occur in young women indicates that hormonal factors are of pathogenic importance This assumption is supported by findings in two cases examined for steroid hormone receptors[7,8]. Both showed a rich content of progesterone receptors and one of them also had oestrogen receptors. Thus, it is possible that pregnancy might have growth-promoting or other effects on this kind of tumour, explaining the concurrent onset of abdominal pain in our patient.

Given the surgical curability of the solid or cystic papillary neoplasm, its distinction from a malignant islet-cell tumour is important in determining the choice of treatment, and ultimately to the well-being of the patient. It is a differential diagnosis to keep in mind whenever a pancreatic tumour occurs in a woman of childbearing age.

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Selective postoperative radioactive iodine treatment of thyroid carcinoma

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In a consecutive series of 234 patients with differentiated thyroid carcinoma of follicular cell origin (Hürthle cell tumors excluded), a radioactive iodine (^{131}I) scan was obtained 3 to 6 months after thyroidectomy and 4 weeks after cessation of thyroid hormone treatments, only if extrathyroidal tumor extension or nodal or distant metastases were present Twenty-one patients (9%) with ^{131}I uptake of 3% or more (group 1) were treated with 150 to 200 mCi of ^{131}I. Forty-four patients (19%) with less than 3% uptake (group 2) and 169 patients (72%) without evidence of metastases or extrathyroidal spread (group 3) were treated only with thyroid hormone. All patients initially underwent total thyroidectomy and modified neck dissection if cervical lymph node metastases were present. Three patients in group 1 and one patient in group 2 had recurrent tumor with a mean follow-up of 8.9 and 8.4 years. There were no recurrences in group 3 with a mean follow-up of 7.2 years. Death rate from thyroid carcinoma was 5% in group 1 (one patient) and 0% in groups 2 and 3. In conclusion, ^{131}I scanning and therapy may be omitted in patients with differentiated thyroid carcinoma in the absence of local tumor extension or regional or distant metastases. Therapy with ^{131}I is not demonstrated to be of benefit in this population of patients. (SURGERY 1989;106:956-9.)

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THE PROLONGED NATURAL history of differentiated thyroid carcinoma makes it difficult to compare the efficacy of various forms of treatment and their influence on survival. Just as there are conflicting data regarding the extent of operative treatment, there is similar controversy over the indications for postoperative radioactive iodine (^{131}I) scanning and treatment [1-7]

For the past 25 years, it has been our policy that only those patients with differentiated thyroid carcinoma with extrathyroidal tumor spread or metastatic disease undergo postoperative ^{131}I scanning and treatment. All patients underwent total thyroidectomy, modified neck dissection for cervical node metastases, and permanent thyroid-stimulating hormone (TSH) suppression. This study is a prospective follow-up examination of 234 patients to assess the efficacy of selective ^{131}I scanning and treatment in differentiated thyroid cancer.

MATERIAL AND METHODS

Two hundred thirty-seven patients—184 (78%) with papillary and 53 (22%) with follicular carcinoma—were treated from 1961 to 1986. All operable patients underwent total thyroidectomy. Modified neck dissection was performed in 52 patients (22%) because of cervical lymph node metastases. All patients received TSH suppressive therapy preoperatively and postoperatively. Postoperatively a total body ^{131}I scan was obtained in 65 patients (27%). Only 21 patients (9%) required therapeutic doses of ^{131}I to ablate remnants of normal thyroid or to treat nodal, lung, or bone metastases. Two patients who never received ^{131}I died 17 days and 4 months after presentation—one with disseminated papillary carcinoma involving regional lymph nodes, lungs, liver, brain, and spinal cord, and one with a locally unresectable papillary carcinoma fixed to the trachea and invading the platysma muscle. A third patient, who had a papillary carcinoma that did not take up ^{131}I, died of disseminated papillary carcinoma 2 years after thyroidectomy. These three patients were excluded, leaving 234 patients for analysis.

Patients were selected for postoperative ^{131}I scanning on the basis of the presence of extrathyroidal tumor ex-

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tension, mediastinal or cervical lymph node metastases, or distant metastases. The scan was obtained 3 to 6 months after thyroidectomy. Thyroid hormone replacement with thyroxine was discontinued 4 to 6 weeks before the scan, and a significantly elevated TSH level was documented. All patients had a TSH level greater than 50, optimally between 75 and 100,[3] before ^{131}I was administered.

A 10 mCi tracer dose of ^{131}I was used for imaging. The interval between dosing and imaging was 72 hours. Patients were treated with ^{131}I when metastatic disease was identified in the cervical lymph nodes, the lungs, or bone, or if uptake was 3% or more of the administered dose. A therapeutic dose, calculated on the basis of ^{131}I uptake, was then administered after hospitalization. Therapeutic doses ranged between 150 and 200 mCi.[8]

A repeat scan was obtained 2 to 3 days after the therapeutic dose in search of uptake in other areas that may have been missed by the 10 mCi dose. Total body scan was repeated 6 months later in all patients to ascertain the absence of further uptake. All patients were treated until metastases disappeared. The maximum cumulative dose of ^{131}I administered was 500 mCi. Once the patient was free of significant uptake, the scans were not repeated unless the question of recurrence arose.

RESULTS

Over the 25-year period, from 1961 to 1986, 234 patients with differentiated thyroid carcinoma were treated according to the previously described therapeutic protocol. They were divided into three groups, and each group was prospectively followed up for evidence of recurrence and mortality.

Group 1 consisted of 21 patients (9%), with ^{131}I uptake of 3% or more, who were treated with 150 to 200 mCi. Treatment with ^{131}I was for ablation of residual thyroid in six patients, for micrometastases in cervical or mediastinal lymph nodes in seven patients, and for lung metastases in eight patients.

Group 2 consisted of 44 patients (19%), with evidence of extrathyroidal tumor spread or metastatic disease at operation, who had less than 3% uptake on a postoperative scan. These patients were treated with thyroid hormone only, and no ^{131}I was administered.

Group 3 consisted of 169 patients (72%) who had no evidence of extrathyroidal extension or metastases. These patients did not undergo ^{131}I scanning, and all of them were treated postoperatively solely with thyroid hormone.

The age, sex, and papillary/follicular distribution in all three groups were similar. The median follow-up was 7 years for groups 1 and 2 and 6 years for group 3. Mean follow-up was 8.9 years for group 1, 8.4 years for group 2, and 7.2 years for group 3. During follow-up, three patients (14%) in group 1 had recurrent tumor, as did one patient in group 2. No patient in group 3 had recurrent tumor. One patient (5%) in group 1 died. There were no deaths in groups 2 or 3.

DISCUSSION

The primary means of treating differentiated thyroid carcinoma is with surgery. Our therapeutic protocol for the past 25 years has consisted of total thyroidectomy, modified neck dissection for cervical lymph node metastases, permanent thyroid hormone replacement and suppression of TSH, and selective ^{131}I scanning and treatment.

Our data would suggest that routine ^{131}I scanning and treatment are not necessary for all patients with differentiated thyroid carcinoma. In the 169 patients without evidence of metastatic disease (group 3), ^{131}I was not administered, and patients were treated simply with thyroid hormone. There were no recurrences and no mortality in this group after a mean follow-up of 7.2 years.

The 44 patients with less than 3% uptake on total body scan (group 2) were also treated solely with thyroid hormone. Only one patient (1.6%) had a recurrence, and there was no mortality after a mean follow-up of 8.4 years.

Radioactive iodine scans were obtained selectively in those patients with extrathyroidal tumor spread or metastatic disease. Therapeutic doses of ^{131}I were administered when total body scans demonstrated more than 3% uptake or when uptake occurred in the cervical lymph nodes, lungs, or bone (group 1). There were only 21 patients (9%) in this group, three (15%) in whom recurrence developed, and one who died. Mean follow-up for this group was 8.9 years.

With the effectiveness of total thyroidectomy and permanent TSH suppression in patients with differentiated carcinoma confined to the thyroid gland, the addition of ^{131}I scanning and treatment seems unnecessary. Because of the policy of selective ^{131}I scanning and treatment, 72% of patients with differentiated thyroid carcinoma in this series were not subjected to total body scanning, and 91% did not require adjuvant ^{131}I therapy. These patients were also spared the need for follow-up scans, as well as the obligatory 4- to 6-week period of hypothyroidism before each scan, during which elevated TSH levels may be contributing to tumor growth.

To summarize our selective policy: postoperative ^{131}I scans are limited to patients with evidence of regional or metastatic disease. Therapeutic doses are only administered in this subset of patients if their scan is positive after total thyroidectomy. Repeat follow-up scans are limited to those with persistent disease or evidence of recurrence. In addition to eliminating obligatory periods of hypothyroidism and repeated radiation exposure, this selective policy has been important in cost reduction. It has also limited the potential for radiation-related complications.

Potential complications of ^{131}I therapy include hematopoietic side effects such as aplastic anemia and leukemia.[9-11] Although most often associated with high cumulative doses of ^{131}I,[10, 11] leukemia has been reported as occurring 1 year after as little as a 100 mCi dose.[12] Pulmonary fibrosis and gonadal damage with decreased spermatogenesis have also been reported.[6, 13, 14] Some authors have suggested that anaplastic conversion of differentiated thyroid carcinoma and development of second malignant tumors may be sequelae of ^{131}I therapy.[14-16] Overall, major complications of ^{131}I treatment are infrequent, and no patient in this series had complications related to this therapy.

It is well established that the percentage of patients who will die of metastatic differentiated thyroid carcinoma is small.[17] Yet it is important to identify these patients because they can be effectively treated with ^{131}I with potential long-term survival.[17] Conversely, it is also important to identify patients with disease in its early stages so that unnecessary ^{131}I scanning and treatment and its associated complications can be avoided. A normal-appearing chest x-ray film and the absence of extrathyroidal tumor spread and lymph node metastases seem to be valid indicators that the disease is in its early stages and that ^{131}I studies and treatment are unnecessary

Of the 10 patients initially seen with pulmonary metastases in our series, seven had an abnormal-appearing chest x-ray film, and eight had evidence of lymph node metastases at operation. In a series from M.D. Anderson Hospital, 101 of 1127 patients with differentiated thyroid carcinoma had pulmonary metastases, and 91% had their conditions diagnosed by means of chest x-ray films.[18] Although infrequent, there is a potential to miss the early diagnosis of pulmonary metastases in the rare patient with tumor limited to the thyroid gland, absent lymph node metastases, and a normal-appearing chest x-ray film. There are no data in the literature, however, to support that there is any advantage in treating occult metastases with ^{131}I before they appear on chest films.[4]

Therefore we conclude that ^{131}I studies and treatment can be omitted in patients with differentiated thyroid carcinoma of follicular cell origin who have a normal-appearing preoperative chest x-ray film and no intraoperative evidence of extrathyroidal tumor extension or lymph node metastases. Patients are maintained with thyroid hormone and are followed up closely with periodic examination of the neck, thyroid function tests, and chest x-ray films.

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DISCUSSION

Dr. John M. Monchik (Providence, R.I.) In your group 1, there were 20 patients who had an uptake of greater than

3%. What percentage of these had evidence of extracentral compartment uptake of the isotope?

Dr. McHenry. Fifteen of the 21 had evidence of uptake outside the thyroid bed.

Dr. Gary B. Talpos (Detroit, Mich.). Could you please comment on whether any of your patients had evidence of multicentricity, capsular invasion, or vascular invasion.

Dr. McHenry. Of the 184 patients with papillary carcinoma, 107 (58%) had multicentric and 67 (36%) had bilateral disease. Of the 53 patients with follicular carcinoma, there were 13 with evidence of angio-invasion.

Dr. Orlo H. Clark (San Francisco, Calif.). I did not hear you mention thyroglobulin. I am somewhat surprised, since I think it is a very sensitive way of detecting persistent or recurrent disease

When it was detected by scan positive, by thyroglobulin positive, x-ray negative, or CT scan negative, they had excellent survival and decrease of thyroglobulin, and subsequent radioactive iodine scans were normal. When the lesion was detected on chest x-ray film or CT scan, there was very poor survival. There was a dramatic and a highly significant difference in the two groups.

Dr. McHenry. We do follow thyroglobulin levels.

Dr. Clark. Did your thyroglobulin correlate with any of your other findings?

Dr. McHenry. The thyroglobulin results did not correlate with the findings in the paper.

Dr. Peter Goretsky (Dusseldorf, FRG). I think it is too provocative to skip scanning in follicular cancer. In our experience, 20% of patients with T-1 stages in follicular cancer already had metastases that could not always be seen on conventional x-ray films I would still recommend routine scanning for all extensive disease and follicular cancer.

Dr. Norman W. Thompson (Ann Arbor, Mich.). I have had the good fortune over the years to work with Dr. William Beierwalters, and now there are more than 720 patients who have been treated at the University of Michigan with radioactive iodine.

Over the years what has impressed me with early scanning (6 weeks after operation) is the detecting of occult pulmonary metastases, particularly in patients with papillary carcinoma.

I think we have accumulated 34 or 35 patients that fall into that group. These patients get treated with one dose of radioactive iodine, either 180 or 200 mCi, and their tumors are invariably ablated completely. But those that are obvious on chest x-ray film, as you described in 8 of 10, often require two or three doses or more and may not always be cured.

I notice that the maximum dosage you gave was 500 mCi, which is in a safe range, but most of the time when you have pulmonary metastases that you can see on chest x-ray film, it is going to require more than that to completely ablate them over a period of years. We continue to scan everybody with papillary cancer at 6 weeks with hopes of detecting lesions as early as possible.

You brought out another significant point. Most of the patients with papillary cancer who have pulmonary metastases also have had cervical lymph node involvement. But that role is not 100%, and we have had patients who had primary tumors and no metastases in the neck but had occult metastases.

I enjoyed your paper, but I must say that we continue to scan everybody. Our tradition has been to scan at least three times in the first 10 years. I think thyroglobulin levels, once the scan is negative, are sufficient and, if normal, eliminate that 6-week period of hypothyroidism that is so distressing to many patients.

Dr. Blake Cady (Boston, Mass.). In contrast to Dr. Thompson, I congratulate you—particularly for being selective about the use of radioactive iodine. I think the next task we have in this disease is to minimize our therapy in that large percentage of patients who are at such low risk for any untoward events happening

I am curious that you use lymph node metastases as evidence of a poor outcome because almost every study that I know of shows that they are not an indicator of poor outcome; other aspects of the primary tumor serve that function.

I wanted to ask you why you did that. If you eliminated lymph nodes as your indicator for scanning, what would your results have been?

Dr. McHenry (closing) If we had eliminated lymph node metastases, we would have missed three patients with pulmonary metastases that were not identified on chest x-ray films.

As I showed, 7 of 10 patients who actually had pulmonary metastases were diagnosed by an abnormal chest x-ray film. The other three with pulmonary metastases were found because a radioactive iodine scan was obtained because they had lymph node metastases.

Book reviews

100 Case Histories for the FRCS

L C Barr, M. R Pittam 215 × 140 mm. Pp. 244 Illustrated 1989. Edinburgh Churchill Livingstone £9 95.

This small book is warmly recommended to all Surgeons in training about to take the FRCS Each case history occupies half the right hand page of the book with adequate room for jotting notes below. The answers to some fairly searching questions are given on the reverse

The selection of case histories and their increasing complexity towards the end of the book is very cleverly done This is an ideal way to be made to think about management, further reading suggestions are made after many of the case histories All the major specialties are covered The opinions given are up to date and balanced and no FRCS candidate can afford to miss the opportunity of 100 mock vivas

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Surgery for the Morbidly Obese Patient

M. Deitel 270 × 190 mm. Pp. 400 Illustrated. 1989 Beckenham Lea and Febiger £45 20

Although critics may regard obesity surgery as not being in the mainstream of current British surgical practice, there are about 40 Consultant Surgeons performing such operations in the UK at the present time For them this book provides a complete and detailed survey of contemporary techniques and attitudes For potential recruits to the art it is an excellent reference book

It is divided into three sections, the first of which gives a basic understanding of obesity, its cause, complications, non surgical management and perioperative risks The second section covers the full spectrum of surgical techniques which have evolved over the past 25 years, giving good details of operative technique, potential complications and management. A fair assessment of temporary surgical measures such as jaw wiring and gastric balloon is included and so is a brief survey of plastic surgical techniques that may be used. Finally the third section emphasizes the importance of care and follow-up including metabolic, gynaecological, obstetric and psychological sequelae The Editor's personal comments on various aspects of techniques are useful and of interest

Throughout the illustrations are good and the text readable. It is a well organized publication which does not burden the reader with masses of references but contains an optimum number sufficient to support the context. All the contributors are North American and write with enthusiasm based on wide knowledge of a subject which originated in that continent and which remains far and away the most active in obesity surgery

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Clinical Obstetrics and Gynaecology; Operative Treatment of Ovarian Cancer

E. Burghardt, J M Monaghan 235 × 155 mm. Pp 215 Illustrated 1989. London Baillière Tindall. £18.50

This volume in the series of Clinical Obstetrics and Gynaecology by 44 contributors provides a ready source book of the latest thinking in the management of ovarian cancer A book of this size with so many contributors is difficult to fuse into an entirely satisfactory whole but the Editors have had some success in achieving their objective of presenting current thinking on the surgical treatment of ovarian cancer

The book is clearly of interest to committed gynaecologists and would be an easy source book to update the knowledge of general surgeons who might unexpectedly be faced with managing such a case.

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Blood Flow in Artificial Organs and Cardiovascular Prostheses

J C. Barbenol, A. C Fisher, J D S Gaylor, W. J Angerson, C. D Sheldon. 240 × 160 mm. Pp 266 Illustrated. 1989 Oxford. Oxford University Press. £35 00

This volume is essentially the proceedings of the Annual Scientific Meeting of the Biological Engineering Society As such it is inevitably heterogeneous and each of its 31 chapters stands alone Two thirds of the more than 60 authors are from the Bioengineering Departments of Glasgow, Leeds and Sheffield. There are several rather loose themes As the title indicates some deal with flow in grafts, through valves and in oxygenators There are also several on the very important topic of interaction between blood and foreign surfaces Because the clinical areas are very varied it is unlikely to be attractive to any one clinical surgeon, but would be of use to the bioengineer who must take an interest in the haemodynamics and biocompatability of prostheses for a variety of clinical subspecialties

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Gastrointestinal Disease: Pathophysiology, Diagnosis, Management. 4th ed.

M. H. Sleisinger, J. S Fordtran. 220 × 285 mm Pp 2027 Illustrated 1989. Philadelphia W B Saunders. £95 00

When Sleisinger and Fordtran was first published in 1973 it immediately became the pre-eminent textbook of gastroenterology in the world, and the fourth edition keeps the book as the best buy in the field. Its excellence lay and lies, not so much in the breadth from 106 chapters by 106 authors (Austria, 1; Canada, 2, USA, 103), as in the combination of biomedical science and clinical practice

A questioning surgeon will find sound guidance on medical aspects of gastroenterology (excluding the liver and children) and will be happy if his medical gastroenterologists are similarly well advised. Non-American surgeons should remember that the picture of alimentary surgery painted in this medical textbook is USA-based Chapter 51 on Operations for Peptic Ulcer Disease, has four and a half pages on gastrectomies, truncal vagotomy and vagotomy and antrectomy, yet only two on 'parietal cell vagotomy without drainage'. Neither selective nor highly selective (proximal gastric) vagotomy is included in Table 53-1 of problems after ulcer surgery With this one caveat, surgeons should see that this book is in their hospital library

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Atlas of Vascular Surgery

C K Zarins, B L Gewertz 288 × 222 mm Pp 320 Illustrated 1989 Edinburgh Churchill Livingstone £79.50

This new atlas of vascular surgery is part of a series, 'Surgical Practice Illustrated', by Dr David Skinner Dr Skinner states in his introduction that a new atlas is necessary owing to the increasing fractionation and specialization of general surgery. There are, of course, several, if not too many, vascular surgical atlases already produced and this one is very much like the rest It is beautifully illustrated and covers a wide range of vascular surgical procedures, associated with a fairly limited and didactic text which possibly does not emphasize sufficiently some of the pitfalls of the various operations or other options which may be available Although it calls itself an atlas of vascular surgery it is confined, in fact, to the treatment of arterial problems and does not mention venous or lymphatic disease Its style is very similar to *Rob and Smith's Atlas of Surgery* and its standard of production is comparable

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Atlas of Bedside Procedures. 2nd ed.

T. J Vandersalm, B. S Cutler, H Brownell Wheeler. 280 × 215 mm. Pp 450. Illustrated. 1989. Boston: Little, Brown and Co £24 95

Practical procedures are best learnt by expert demonstration followed by supervised practice However, few of us will not have turned to a reference book for reassurance that we have not forgotten any vital steps or hazards Such a reference should be clear and concise, well illustrated and up to date.

The *Atlas of Bedside Procedures* ably fulfils these criteria. The repertoire of 50 procedures is greater than the title suggests and includes several which require fluoroscopic control and several best performed in theatre. The basic techniques are well described including those life saving procedures at which all doctors should be competent such as venous cutdown, endotracheal intubation, defibrillation, and cricothyroidotomy It is worth reading through those which have not been recently practised. Arterial and venous cannulation for access and measurement is well covered and the Seldinger technique widely used Percutaneous biopsy techniques are described and some procedures (aortic balloon pump, Greenfield Caval Filter) are best reserved for the specialist.

Each chapter begins with an equipment list followed by a didactic step-by-step account with well-placed clear line drawings which, as often, are much better illustrations than photographs The methods described are safe and reliable and I could find little to quibble about Finally there is a comprehensive list of complications and guidance on their prevention and management

This book is a valuable practical manual which would be more useful when kept in the emergency room or intensive care ward than in the library or at home. Unfortunately the binding, of the paperback version at least, is insufficiently robust to survive its purpose and the pages are already falling out of my copy.

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A Guide to Practical Procedures in Medicine and Surgery

H A F. Dudley, J R. T Eckersley, S Paterson-Brown 235 × 155 mm. Pp 179 Illustrated 1989. Oxford Heinemann Medical Books £12 50

The uncertainty attending early attempts at practical procedures is an anxiety for many junior doctors. As the authors acknowledge there is no substitute for doing a procedure, preferably after demonstration and under supervision, but this ideal is often unattainable and an inexpensive guide is welcome

The illustrations by Gillian Lee are excellent although on one page, the captions do not match the illustrations and there are a few typographical errors Many of the drawings would tolerate substantial reduction in size with no loss of detail: tracheostomy is described with four attractive drawings occupying only one page whereas excision of a sebaceous cyst occupies two full pages. The content is pitched at an appropriate level with useful information on venous access, resuscitation, local and general anaesthesia, orthopaedics and intubation of a variety of body cavities. The guide would be improved if alternative techniques and equipment were described, for example chest intubation depends on the availability of an Argyle chest drain. The section on minor operations is disappointing in its advocacy of dated procedures Deroofing and packing of abscesses delays healing compared with simple incision and drainage and phenol ablation is a more reliable and simpler technique than excision of the nail bed With characteristic elan, repair of a penetrating cardiac wound also features but is, reasonably enough, accompanied by the admonition to seek more senior help. For the inexperienced or isolated novice the book shows one way of addressing many common procedures but it would be improved if it were more compact and other methods included.

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Assessment of short saphenous vein

Sir

The article by S. N Vasdekis *et al* (*Br J Surg* 1989, **76** 929–32) addresses the problem of the ligation of short saphenous varicosities (SSV) and the localization of the short saphenous-popliteal junction (SS-PJ) The authors highlight the high recurrence rates following short saphenous surgery and point out that this is probably due to inaccurate localization of the SS-PJ. They report that duplex scanning is accurate to within ±2 cm in 96 per cent of cases and that the next best method of localization is the Doppler ultrasound, accurate within the same limits in only 64 per cent of cases.

As a surgical trainee the need to place the skin incision as close as possible to the SS-PJ is stressed and from the above paper the use of duplex scanning would appear to be superior to other clinical methods However the paper omits to comment on two points from their own data In the series, six patients had SSV that emptied into the long saphenous vein which were detected by duplex scanning and used in their calculation of accuracy for that mode of investigation. They do not mention whether these SSV were detectable by the Trendelenberg test at the groin, which one might expect

Secondly from their own data shown in *Figure 4*, it is obvious that without any form of investigation an incision placed at 4.5 cm above the knee joint would be within ±2 cm of the SS-PJ in 45 out of 64 (70 per cent) of all cases and 78 per cent of cases of SSV with drainage into the popliteal vein, indeed accuracy to ±1 cm at this point is 52 per cent compared with 50 per cent with the duplex scanner.

If the recommendations of this paper are to be of value surely these points should be discussed or one might deduce that in hospitals without a duplex scanner a 'blind' incision without clinical assessment should be performed!

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Author's reply

Sir

We appreciate the observations of Mr Menzies However, because the recurrence rate of operations on the short saphenous vein was up to 40 per cent in 1970 we introduced on-table venography[1]. This one-shot varicogram clearly demonstrated the anatomy and because the level and pattern of termination was found to be so variable the method is used for all operations on the short saphenous vein. This allowed a small accurately placed incision above the popliteal crease with the reassurance of knowing the precise anatomy In 1100 operations using this technique there have been less than 20 known recurrences Radiography should be available in all theatres where surgery is performed. The object of this study was to test the accuracy of other methods which are sometimes employed for planning surgery on the short saphenous vein

Using Mr Menzies' 'blind' incision, seven of the 64 legs would have had an unnecessary dissection of the popliteal fossa and 30 per cent would have been unsuccessful unless he added additional exploratory incisions or made major extensions to his incisions. We do not believe he would accept such a failure rate or, alternatively, that his patients would accept multiple, extensive and sometimes unnecessary explorations of their popliteal fossa

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Abdominal aortic aneurysm

Sir

The paper 'Abdominal aortic aneurysm repair in the over eighties' (*Br J Surg* 1989, **76**. 1018–20) which has been recently published contains some serious misrepresentations of the CEPOD Report[1]

CEPOD did not recommend or even suggest that patients aged over 80 years with abdominal aortic aneurysms should not be operated on.

The recommendations of CEPOD, on pages viii and ix of the Report, relevant to the problem of the aortic aneurysm in the elderly are No. 5, which stresses the importance of adequate resuscitation and management of coexisting disease, No 6, which emphasizes that Consultants or Senior Registrars should be involved in decisions regarding operations in the elderly; No 7, which states the decision *not* to operate is difficult and should not be made without Consultant Surgeon and Consultant Anaesthetist involvement; No 10, which recommends that operations be only performed by Consultants, or juniors, with appropriate specialist expertise, in the case of abdominal aortic aneurysm with expertise in Vascular Surgery. There is no recommendation that any category of patients should be refused surgery solely on the grounds of their age.

Within the CEPOD Report the management of abdominal aortic aneurysm is discussed on pages 43 and 44 and again on page 59, it is pointed out that aneurysms were operated on by inexperienced and inappropriately skilled surgeons and that 'vascular assessors commented adversely on operations for ruptured aortic aneurysms in patients aged over 80 and on elderly patients with known comorbidity' Mr R N Baird, who is a senior co-author of the paper in *The British Journal of Surgery* was one of the Vascular Assessors for the CEPOD Report

All the recommendations about the management of abdominal aortic aneurysm highlighted in the CEPOD Report are confirmed by findings from Bristol, it is confirmed that abdominal aneurysms in the elderly are best managed by Vascular Surgeons operating in an optimum environment The Bristol Study confirms and vindicates CEPOD The final sentence of the article in *The British Journal of Surgery* is however quite untrue, it is a misrepresentation of the CEPOD Report and it should be withdrawn.

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National Confidential Enquiry into Perioperative Deaths
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1. Buck N, Devlin HB, Lunn JN. *The Report of a Confidential Enquiry into Perioperative Deaths* London· Nuffield Provincial Hospitals Trust and The Kings Fund, 1987

Author's reply

Sir

Presumably an analysis of the deaths reported to CEPOD caused Mr H B Devlin, author of the surgical section, to include adverse comments on operations for ruptured aortic aneurysms in patients aged over 80 years The arguments would have been persuasive if data had been collected from survivors, a design flaw which has since been remedied in the NCEPOD protocol.

Our paper showed that the lives of some of these patients can be saved by operative repair We aimed to provide more acceptable alternatives to the pejorative CEPOD comments about octogenarians. The issues have been vigorously debated for more than 20 years, and surgical opinion evolves with each new report We stand by our article

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Management of ingrowing toenail

Sir

I was pleased that Mr W. R. Murray[1] advises segmental phenol ablation for established ingrowing toenails, but sorry that he seems to have reviewed only the medical literature and ignored the chiropodial literature.

To set the record straight, the procedure of segmental phenol ablation was proposed by chiropodists in 1945[2], and was being widely practised by chiropodists when Mr Murray in 1975 was still advocating avulsions and Zadik operations[3]. Cooper[4] reported the results of 1200 phenol procedures in 1965!

Further, the results of phenolization performed by chiropodists have been shown to be as good, if not better than the results achieved by surgeons[5]. I feel it important that the role of the chiropodists in the development of this procedure is acknowledged.

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Toxic megacolon and perforation caused by Salmonella

Sir

The report by Gill *et al.* (*Br J Surg* 1989; **76**: 796), of a case of toxic megacolon and perforation caused by *Salmonella*, included no mention of amoebic colitis, a known cause of toxic megacolon[1,2]. The histology of the colectomy specimen of their patient, reported as 'consistent with *Salmonella* colitis' was evidently that of severe non-specific inflammation, and therefore equally consistent with the entirely non-specific histology of amoebic colitis when the trophzoites of *E. histolytica* have not been identifiable in the sections examined[3]. There are numerous references to the ease with which these parasites can be overlooked in sections that have been only stained by routine haematoxylin and eosin[4–6], and the need to employ histochemical stains such as PAS has consequently often been stressed[3,7,8].

The year-long history of episodes of bloody diarrhoea in this patient is not entirely consistent with a *Salmonella* infection, and so it would be of interest to know how an amoebic origin for the patient's symptoms had been excluded. Admittedly he has remained well following the sub-total colectomy, but since the whole of the ulcer-bearing part of his colon was resected can we be sure that he has not been an instance of the cure by surgery of fulminant amoebic colitis?

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Modified sham-feeding and pentagastrin stimulated secretion

Sir

Gilly *et al.* (*Br J Surg* 1989; **76**: 946–8) report a comparison of modified sham-feeding and pentagastrin stimulated secretion for the assessment of gastric function before and after parietal cell vagotomy. Unfortunately their paper is marred by a very serious problem in the methodology, and by a blinkered interpretation of their data.

It is surprising to see that they compared modified sham-feeding with pentagastrin stimulation in the same subject on the same day. Most authors who wish to compare these two stimuli would perform the tests on separate days and start with basal secretion before each stimulus. How can we assess the pentagastrin stimulated output, when this follows on from and may include part of the response to modified sham-feeding?

The authors present the results of the correlations between the different tests simply in terms of *P* values. If we are to believe their contention that pentagastrin stimulated secretion can replace modified sham-feeding in the assessment of vagotomy, the authors must supply data which describe the relationship between these variables. The size of the *P* value does not help.

The authors' monolithic discussion concludes with the statement that modified sham-feeding is unlikely to add to the information provided by pentagastrin stimulated acid output. The authors do not consider the alternative viewpoint, that pentagastrin stimulated output has little to add to the results of modified sham-feeding in the postoperative patient. If the aim of postoperative testing is to determine the presence or absence of residual vagal inervation, it seems more logical to use a test which relies entirely on vagal activity. The authors do not provide any data on the relative accuracy, specificity or sensitivity of modified sham-feeding or pentagastrin stimulation for the detection of patients with residual intact vagal fibres

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Author's reply

Sir

We do not say that modified sham-feeding is of no value In the Discussion it states: 'However, [this test is] a cumbersome and time-consuming method, which requires the attentive participation of the patient, who must be asked not to swallow food particles. Thus the *cost–efficiency* ratio and therefore the usefulness of the test can be questioned when it is used in clinical practice ...'

In the same way, for the sake of simplicity and acceptability by the patient it seems better to perform the three tests consecutively on the same day. Furthermore it can be considered that the alterations due to inter influences of the test are likely to be less than the day-to-day variability of the secretory parameters.

The assessment of the completeness of vagotomy is an old and always unsolved problem. We just say that there is a close relationship ($r_s = 0.48$, $P < 0.01$) between post- and prepentagastrin-stimulated acid output and that this correlation was not noticeably reinforced when premodified-sham feeding-stimulated acid output was added ($r_s = 0.49$). Indeed, the alternative suggestion to use the modified sham-feeding test in place of the pentagastrin-test for the assessment of the completeness of vagotomy could be considered. However the latter is easier to perform and does not require an active participation of the patient.

Finally, specificity and sensitivity of a test can only be calculated when a 'gold standard' is available. Is there any reference method to detect patients with residual intact vagal fibres?

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Notices and announcements

10–12 January 1990
Surgical Research Society Meeting
Liverpool, UK
Information Mr C R. Mackie, Dept of Surgery, University of Liverpool, PO Box 147, Liverpool, L69 3BX, UK

17–22 January 1990
Introduction to Endocrine Investigations
Newport Beach, California, USA
Information Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

19–21 January 1990
26th Head and Neck Course
Liverpool, UK
Information· Professor P. M. Stell, Dept of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, UK

20–21 January 1990
Hong Kong Surgical Forum
Hong Kong
Information. Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

28 January–8 February 1990
The Biological Basis of Radiotherapy
London, UK
Information: The British Council, Courses Dept, 65 Davies Street, London W1Y 2AA

4–9 February 1990
HIV and AIDS: Management and Control
London, UK
Information The British Council, Courses Dept, 65 Davies Street, London W1Y 2AA

4–10 March 1990
Cancer in Children
London, UK
Information· The British Council, Courses Department, 65 Davies Street, London W1Y 2AA, UK

11–13 March 1990
2nd Surgical Masterclass of the Royal College of Surgeons of Edinburgh
Aviemore, UK
Information Mrs Maureen Webb, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

15–18 March 1990
2nd World Congress of Surgical Endoscopy, Ultrasound and Interventional Techniques
Atlanta, Georgia, USA
Information: Program Committee, SAGES, World Congress on Surgical Endoscopy, Suite 409, 1271 Stoner Ave, Los Angeles, CA 90025, USA

19–29 March 1990
Advances in Neurosurgery
Glasgow & Edinburgh, UK
Information Courses Department, The British Council, 65 Davies St, London W1Y 2AA

28–30 March 1990
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Cardiff, UK
Information The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

1–6 April 1990
Clinical Genetics
Cardiff, UK
Information· British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

2–12 April 1990
The Clinical Medicine of Later Life: the Scientific Basis of Practice
Oxford, UK
Information The British Council Courses Dept, 65 Davies Street, London W1Y 2AA, UK

27–28 April 1990
The 3rd International Symposium on Gynaecological Endoscopy
Oxford, UK
Information: Metaphor Conferences & Meetings, 21 Kirklees Close, Farsley, Pudsey, West Yorkshire LS28 5TF, UK

2–4 May 1990
17th Biennial Congress of the Association of Surgeons of South Africa in Bloemfontein
Bloemfontein South Africa
Information: DrGF Ferreira Dept of Surgery, (G72) Univ. of the OFS, Box 339, Bloemfontein 9300, Republic of South Africa

9–12 May 1990
3rd International Symposium on Echocardiography and Doppler in Cardiac Surgery
Vienna, Austria
Information W Mohl, c/o Interconvention, A-1450 Vienna, Austria, +43/1/23 69/2642

29 May–1 June 1990
Peripheral Vascular Disease
London, UK
Information The British Council, Courses Department, 65 Davies St, London W1Y 2AA

5–9 June 1990
European Association for Gastroenterology & Endoscopy: European Digestive Disease Week
Vienna, Austria
Information Mondial Congress, Faulmanngasse 4/11 A-1040 Wien, Austria

8–9 June 1990
3rd Annual Meeting of The Surgical Infection Society
Antwerp, Belgium
Information· Professor A. Hubens, University Dept of Surgery, Stuivenberg General Hospital, Lange Beeldekenstraat 267, B-2008 Antwerp, Belgium

11–14 June 1990
6th International Congress on Breast Diseases
Boston, Massachusetts, USA
Information 6th International Congress Secretariat, c/o Office of Continuing Education, Tufts University School of Medicine, 136 Harrison Avenue, Box 36, Boston, MA 02111, USA

13–16 June 1990
5th European Symposium on Gastrointestinal Motility
Augsburg, FRG
Information Professor M Weinbeck, Dept. of Internal Medicine III, Zentralklinikum, D-8900 Augsburg, FRG

20–23 June 1990
Annual Meeting of The Endocrine Society
Atlanta, Georgia, USA
Information Ann singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong
Information. The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

15–21 July 1990
1990 Surgical Updating
Milan, Italy
Information· Segreteria Organizzativa, MGR, Via Servio Tullio, 4-20123 Milano, Italy

14–15 July 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

24–28 June 1990
XIII Biennial Meeting of I.S.U.C.R.S.
Graz, Australia
Information Miss D Strauss, Executive Secretariat, c/o Indru T. Khubchandani, 1275 S Cedar Crest Boulevard, Allentown, PA 18103, USA

24–29 June 1990
The 3rd Oxbridge Organ Transplantation Course
Oxford, UK
Information· British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

22–27 July 1990
FASEB Summer Research Conference 'Physiology and Pathophysiology of the Sphlanchnic Circulation'
Colorado, USA
Information. Federation of American Societies for Experimental Biology, Splanchnic Circulation Conference, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

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Br. J. Surg. 1990, Vol. 77, March, 242–242

Assessing patients with head injury

Head injuries are common, accounting for 300 hospital admissions per 100 000 of the population per year and comprise up to 20 per cent of acute surgical admissions[1]. As we enter the nineties where do we stand with head injury management in the UK? Sad to say, arrangements for head injury care in general are haphazard and have signally failed to keep pace with advances in diagnostic imaging, intensive therapy and organization of trauma care. As a result, in much of the UK standards of head injury care now fall short of those that apply in Northern Europe. The problem is related less to insufficient resources than to a failure to organize existing services. This is especially unfortunate because head injury management is well suited to a systematic, protocol driven approach.

The goals of head injury management are to prevent or reverse secondary insults to the injured brain and to provide the best milieu for the recovery of dysfunctional or damaged brain tissue. The secondary insults of most concern are systemic arterial hypotension and hypoxaemia, brain compression from haematomas, and raised intracranial pressure[2]. The management protocol is based on two pivotal principles. The Glasgow Coma Scale provides a reliable and widely accepted means not only of assessing the level of consciousness but also of stratifying patients into management groups. The presence of a skull fracture greatly increases the statistical risk of an intracranial haematoma being present, particularly in patients with preserved consciousness[3].

In the accident and emergency department the former practice of admitting patients who had been knocked out and discharging those who had not is outmoded and inefficient[4]. The level of consciousness should be assessed on the Coma Scale on admission and after resuscitation and all patients who score less than the full 15 points should be admitted, even if there is a suspicion that the brain impairment is due to alcohol or drugs. If there is any evidence of skull fracture on skull radiographs (AP lateral and Towne's views), periorbital or retroaural bruising or leakage of cerebrospinal fluid from nose or ear, the patient must be admitted to hospital. The same applies to patients who have focal abnormal neurological signs, seizures and severe persistent headache and vomiting (especially in young children in whom the association between skull fracture and intracranial haematoma is less strong). Clinical common sense will also lead to admission of patients with medical problems concurrent with the head injury, such as diabetes or disorders of blood clotting. Patients who are alert with no skull fracture, no fits and no abnormal signs may be discharged even if they have been previously briefly unconscious following a concussional head injury[5]. Adoption of such an admission policy in Edinburgh in 1982 reduced the number of head injury admissions by several hundred *per annum*, saved more than 2000 patient bed nights per year and did not result in any increase in the number of late-presenting intracranial haematomas[6].

Patients who do not open their eyes to pain (E1), do not obey commands (M5 or less) and do not utter recognisable words (E2 or less) are by definition in coma. They are classified as having severe head injuries and 40 per cent of them have intracranial haematomas, regardless of whether the patient's condition appears to be stable, deteriorating or even improving. Such patients need a computed tomography (CT) scan for the diagnosis of the haematoma as soon as they can be moved safely, even if this means transfer to another hospital. Patients with moderate and minor head injuries, scoring 9–12 and 13–15 on the Glasgow Coma Scale respectively, have a much smaller chance of harbouring an intracranial haematoma but that risk is increased manyfold by the presence of a skull fracture. Patients with a skull fracture who score less than 15 points on the Glasgow Coma Scale, or who have neurological deficit, seizures or even severe headache and vomiting, should have a CT scan within 24 h of injury. As CT equipment is being installed in an increasing number of district general hospitals this policy should become possible nationwide. In a well run system the majority of extradural haematomas should be detected in patients who are still conscious. In Edinburgh introduction of a more liberal policy for CT scanning resulted in the proportion of extradural haematomas detected in non-comatose patients rising from 41 to 68 per cent with halving of the mortality

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rate and major improvement in the morbidity rate[7]. A policy of early CT scanning based on the risk factors (Glasgow Coma Scale and skull fractures) reduces one major cause of secondary brain damage, namely compression by haematomas. What of the other forms of secondary insult?

More than 50 per cent of patients with severe head injury have multiple injuries, setting the stage for blood loss and arterial hypotension, chest and lung injury and hypoxia. Brain injury alone may produce hypoxia due to shunting and diffuse intravascular coagulation. On admission, 30 per cent of severely head injured patients are hypoxaemic and 15 per cent are hypotensive[2]. During transport between hospitals and even between different departments within the same hospital, secondary insults can easily occur in the form of arterial hypotension, hypoxaemia and raised intracranial pressure. These problems are more likely to occur in patients with a high injury severity score, raising questions about the adequacy of initial resuscitation[8].

For the adequate assessment of the head injured patient the Glagow Coma Score should be used for triage; skull radiographs should be used in non-comatose patients to locate skull fractures, to determine the risk of intracranial haematoma, and also the risk of intracranial infection due to a penetrating injury (revealed by the presence of intracranial air or a depressed skull fracture); CT scanning should be used for the diagnosis of intracranial haematoma and the presence of intracranial air, and the bone window settings are very useful for confirming the presence of a depressed fracture that may not be easily seen on a plain radiograph. To assess neurological function, the Glasgow Coma Score, including the best and worst motor scores on each side, as well as the pupil size and reaction and reflex eye movements (oculocephalic or oculovestibular), will provide the essential clinical information. For detecting secondary insults, recordings must be made of temperature, heart rate, blood pressure (using intra-arterial measurement in comatose patients), oxygen saturation (by pulse oximetry), arterial oxygen and carbon dioxide tensions and, in the comatose patient, intracranial pressure, may be monitored directly under neurosurgical advice. During transport it is important to monitor blood pressure and oxygen saturation by pulse oximetry.

The days of admitting obtunded head injured patients, observing them and later transferring those who lapsed into coma to the regional neurosurgical unit should be a thing of the past. Each region, district or area should have a clear policy on head injury management based upon ready access to CT and neurosurgical advice and help. Each regional neurosurgical unit should be provided with sufficient beds and staff to admit severe and complicated head injury cases from the geographic referral area, and should also offer advice and help in cases deemed insufficiently severe to warrant transfer.

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Br. J. Surg. 1990, Vol. 77, March, 243–244

Meta-analysis

The most convincing evidence which can be obtained to assess the efficacy of a treatment method comes from a clinical trial, which would be randomized, subject to fastidious quality control, and, crucially, have a sufficiently large sample size to detect moderate but clinically important effects. Unfortunately it requires very large trials to detect such effects. For example, if an extremely effective prophylactic agent was available which could reduce an operative complication rate from 10 per cent to 5 per cent, thereby preventing 50 per cent of such complications, then over 1000 patients would need to be studied to give an adequate power to detect this benefit (i.e. to give a 90 per cent chance of achieving $P<0{\cdot}05$). To detect smaller effects, which could still represent very important advances in clinical care, requires yet larger numbers.

The need for such trials involving many thousands of subjects is being realized increasingly in cardiovascular disease[1], but as yet they are exceedingly rare in surgery. Instead, what one tends to find when reviewing an important clinical question is that the literature is littered with a large number of small trials, many of which appear to be contradictory, and no one of which is adequate to give a conclusive answer to the question under consideration. This situation is well illustrated in the area of antibiotic prophylaxis in biliary tract surgery by the introduction to the meta-analysis reported in this issue by Meijer *et al.*[2].

Meta-analysis is a branch of statistical methodology which has been developed in an attempt to bring a degree of rigour to the important and difficult task of drawing a consensus from the results of a large number of small trials, each addressing a closely related clinical question. In essence one adds together the results of all relevant trials, and, not surprisingly, this approach is often criticised for 'mixing apples and oranges'. Even trials which are broadly similar can differ substantially in terms of the populations studied (age, social class, severity of disease, etc.) and in factors such as the timing of initiation of treatment, the dosage schedule, compliance, and even the type of drug within a class. Thus it is almost inevitable that a meta-analysis will underestimate the benefit of a treatment given under its optimum conditions. However, the rationale behind the approach is the assumption that if a treatment is effective then the treatment effects observed in different trials will tend to go in the same direction. One would certainly expect there to be systematic differences in the magnitude of the treatment effects observed in trials with different patient populations and with different modes of administration, but as long as the direction is consistent, then the large numbers which result from pooling will tend to cancel out random variability, and the trials will tend to reinforce each other.

It is possible to guard against an over-simplistic pooling of trials in a situation where a treatment is harmful to one group of patients and beneficial to another. This can be done either by performing a test of heterogeneity over the trials under consideration[3], or else by creating broad groupings of trials and making comparisons between these groupings[4].

If one is prepared to accept the underlying concept of looking for treatment effects which tend to point in the same direction, then one immediately hits the crucial practical, and indeed methodological, question of how to select the trials for inclusion in the meta-analysis. Ideally one wishes to include all relevant trials, whether published or not. At the very least one must aim to achieve an unbiased random sample of all relevant trials. A major difficulty here is the widely recognized phenomenon of publication bias[5]. The medical literature is very much biased towards positive trials, both because investigators are more strongly motivated to report such trials, and also because editors are more likely to accept such reports for publication. If one simply reviews the published literature, there is a risk of reaching a distorted conclusion. Thus the meta-analyst must devote time to scanning conference proceedings and to contacting investigators known to be active in the relevant area in an attempt to locate less well publicized results. This task, which is easily the most tedious and time consuming part of the preparation of a meta-analysis could be greatly simplified if there were comprehensive registers kept of all clinical trials. Such registers do already exist in certain areas[6], and with sufficient scientific pressure and financial support they could perhaps be enforced by making registration a prerequisite for obtaining ethical approval to undertake a trial. Certainly such moves would enormously enhance the credibility of the conclusions drawn from meta-analyses.

Another problem, which would also be helped by the registration of trials, is multiple reporting. This is certainly not unique to surgery, but there is a strong

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tendency to report the results of surgical trials at regular intervals as the sample accumulates. Thus there might easily be a single trial reported in several conference proceedings, with a steadily increasing sample size, and with authors changing as research registrars come and go, making it difficult to ensure that a given patient only appears once in an overview. Such repeated reporting of the results of ongoing trials is bad statistical practice at the best of times, but it does raise particular problems in the context of meta-analysis.

A further controversial area is whether one should exclude trials from a meta-analysis on methodological grounds. There is general agreement that one should restrict attention to randomized trials, for otherwise one could easily introduce biases of such a magnitude that they would dwarf the relatively subtle treatment effects which a meta-analysis is designed to detect. But how, for example, should one treat a trial which has a high proportion of subjects lost to follow-up? The general consensus appears to be that one should consider all randomized trials, because to assess the quality of a trial introduces so many subjective factors that two meta-analyses of the same question might easily reach very different conclusions. Chalmers and colleagues[7] however take a rather different view. His group has a vast experience in meta-analysis, and they argue that the quality of each trial must be measured so that the papers can be listed in order of quality, and sensitivity analyses carried out to determine if the poor quality of some of the randomized trials is distorting the results. This is achieved in practice by applying a carefully developed scoring system to assess the quality of a clinical trial report[8]. Whichever view one takes, there are strong arguments in favour of raising the standards of design and execution of clinical trials in general, and for journal editors to be more receptive to well conducted negative studies.

An interesting question, raised by Meijer *et al.* and answered in the negative[2], is whether meta-analysis can replace future trials. I do not believe that many would argue that it can or should. However, I do believe that meta-analysis has an invaluable role to play, both now and in the future. Without doubt there are many limitations with the approach, as is clear to both its advocates and its critics. However, before dismissing the technique, the critics should remember that the approach is in itself a response to current limitations in clinical trials. Imperfect as it is, it is the best available approach to making sense of a large number of individually inadequate trials. Even in its current state of development, meta-analysis can throw considerable light upon important clinical questions, as is ably demonstrated by Meijer *et al.*[2]. Future developments, such as the establishment of registers of all randomized trials, will further enhance the usefulness of the approach, and any spin-offs in terms of a heightened awareness of the inadequacy of many trials currently in progress can only be a further bonus.

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Br. J. Surg. 1990, Vol. 77, March, 245

Inheritance of colorectal cancer susceptibility

Although dietary factors are clearly implicated in the aetiology of large bowel malignancy, there is substantial evidence to suggest that susceptibility to colorectal cancer is inherited. Many studies[1,2,3] have shown familial clustering of benign and malignant colorectal neoplasms which is not restricted to the syndrome of hereditary non-polyposis colorectal cancer. Lovett[1] noted a slight excess of colorectal cancer in the spouses of affected individuals but subsequently it has been shown that familial clustering of cases cannot be accounted for by the simple hypothesis of common exposure to environmental carcinogens[3,4]. The data support the existence of a gene defect which results in colorectal adenomas and carcinomas with a population frequency of 19 per cent and which is transmitted in a Mendelian dominant mode[3]. In addition, it appears that very few cancers occur in patients who have not inherited a predisposition to large bowel neoplasia. If true, this has resounding implications for screening and early detection of premalignant and malignant colorectal neoplasms.

If there is a heritable colorectal cancer gene, the techniques of modern molecular biology may eventually be able to provide a simple screening procedure involving only a blood test. This would identify those with a gene defect predisposing the large bowel epithelium to the effects of faecal carcinogens. Dietary manipulation seems unlikely to be practical and so such individuals could be enrolled in intensive clinical screening programmes. Such a screening protocol seems eminently desirable for its efficiency and presumed sensitivity. However molecular biologists need clinical data which not only confirm that a colorectal cancer gene does actually exist, but also identify those patients who have inherited it. Clearly not all individuals with the gene defect will develop colorectal cancer and so there is a pressing need for a full description of the 'colorectal cancer gene' phenotype. There are already some pointers as to what such a phenotype might be.

Skin tags are more common in patients with colorectal adenomas than in the general population[5]. It seems unlikely that gut carcinogens should also have an effect on skin tag formation and so such patients may have inherited a defect in a gene with pleiotropic effects involving skin and colonic epithelium. Mandibular osteomas are common in patients with familial adenomatous polyposis (FAP) and these lesions also occur with a higher frequency in patients with apparently non-familial colorectal cancer than in a control population[6]. This suggests that the 'colorectal cancer gene' may actually be the gene for FAP (the so-called *apc* gene) but perhaps carrying a different class of mutation within it. There is molecular genetic evidence to support this hypothesis since *apc* gene deletion has been shown to occur in a high proportion of colorectal carcinomas[7]. If the *apc* gene on chromosome 5 is involved in the inheritance of susceptibility to colorectal cancer then other features of FAP may be prevalent in colorectal cancer patients.

In this issue, Iwama and colleagues[8] examine the association of congenital hypertrophy of the retinal pigment epithelium (CHRPE) and FAP. They, and others[9], have demonstrated the prevalence of this phenotypic marker in FAP patients. If there is a class of inherited *apc* gene mutation which predisposes to colorectal cancer, then CHRPE lesions may occur with undue frequency in patients with large bowel malignancy.

It is clear that the diagnostic work-up of patients with colorectal neoplasms should include a careful family history but studies to delineate the clinical phenotype of the putative colorectal cancer gene are now also required.

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Metabolic effects of cancer

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The potential causes of deranged metabolism in cancer are discussed with emphasis on changes in energy metabolism of glucose, fat and protein. The implications of these changes for the treatment of cachexia are then considered

Keywords: Cancer, cachexia, metabolism, glucose, fat, protein, parenteral nutrition

Cachexia is commonly the cause of death in cases of advanced malignancy[1], and cancer patients who have lost a significant percentage of their body-weight before surgical treatment are subject to a much greater risk of postoperative mortality and morbidity[2–4]. There is no doubt that reduced oral intake resulting from anorexia or obstruction of the gastrointestinal tract plays a very significant role in the development of the cancer cachexia syndrome. However, whereas the metabolic response to uncomplicated starvation acts to limit the consumption of host reserves, in the cachectic cancer patient there is often an accelerated mobilization and oxidation of energy substrates and loss of nitrogen[5–7]. These changes are a consequence of alterations in intermediary metabolism associated with cancer[8].

Understanding the metabolic response to cancer has become increasingly important over the last two decades with the introduction of effective and safe parenteral nutrition techniques[9]. It is now possible to provide sufficient calories and nitrogen to all cancer patients, but the metabolic milieu associated with advanced cancer may retard the restoration of lean body mass[10] In the following review the manner in which malignant tumours affect host metabolism will be presented, and the effectiveness of the available therapeutic options will be discussed.

One consistent feature of data from metabolic studies in cancer patients is the range of response between individuals, even when comparing those with the same diagnosis and stage of disease[11]. The interpretative difficulties are compounded by many reports comparing small heterogeneous groups of cancer patients with equally small groups of controls, which may well be poorly matched for age or weight loss. To overcome some of these problems laboratory models have been developed in which malignant cells of identical genotype are transplanted into genetically uniform animals[12]. However, the growth dynamics and tumour-to-host weight ratios frequently do not resemble those observed in patients, and this review will present mainly data from patient studies.

Changes in energy metabolism

The hypothesis that tumour bearing increases energy expenditure and results in a cumulative negative energy balance and progressive weight loss has been exhaustively investigated, and there is now a substantial body of supportive evidence. Bozzetti *et al.*[13] studied a heterogeneous group of patients with advanced tumours and found a highly significant correlation between the resting metabolic expenditure (RME) and the magnitude of weight loss, and other groups of researchers have similarly found elevated RMEs in patients with cancer cachexia[14–18]. There are a few anecdotal reports of cases in which successful antineoplastic therapy has reduced energy expenditure in hypermetabolic patients[14,18], suggesting that the presence of the tumour itself is capable of elevating the RME. However, hypermetabolism is not an invariable finding in cancer patients who have lost weight, with large series having been reported recently which have failed to demonstrate a significant increase in the resting metabolic rate of cachectic cancer patients when compared with patients with weight loss of a similar magnitude due to benign disease or with weight-stable cancer patients[19,20]. In a series consisting of 200 patients with a variety of tumour types 29 per cent had a resting metabolic expenditure that was 10 per cent higher than that predicted by the Harris–Benedict equation, 31 per cent were found to be hypometabolic using the same criterion and no relationship was demonstrated between RME and weight loss or tumour burden[21].

Although some of the disparity in the findings of these studies is no doubt a reflection of differences in experimental material and methodology, it is likely that they are reflecting a true heterogeneity of response to the tumour bearing state. It is now clear that cancers arising from certain tissues, such as sarcomas[22], leukaemias[23] and bronchial carcinomas[24], frequently provoke a hypermetabolic response, whereas patients with pancreatic and hepatobiliary tumours tend to be hypometabolic[25].

Many cancer patients with advanced disease have a reduced caloric intake. In normal people or in patients with benign disease, semistarvation is attended by a reduction in RME[26,27], so in an undernourished cancer patient even a normal metabolic rate represents a failure of this adaptive response[14,28].

The mechanism by which malignant tissue alters the energy expenditure of the host is not clear It is unlikely that increased energy consumption by the tumour itself is responsible in human tumours as it is rare for tumours to account for more than 5 per cent of body weight[13]. More plausible is the hypothesis that mediators are released by some cancers which alter host metabolism[29,30], and some of the changes that may occur are discussed in subsequent sections.

Changes in glucose metabolism

There are many reports describing an increased rate of endogenous glucose production in cancer patients[11,22,23,31–33] (*Figure 1*), and considerable research effort has been directed towards determining the mechanism and significance of this occurrence. It is clear that the magnitude of the increase in glucose turnover is influenced by tumour stage[6,35] and histology, and that it is associated with cancer cachexia[36]. In this section, some of the observations made in cancer patients of changes in glucose metabolism will be summarized and the implications that these have on energy balance will be discussed.

Gluconeogenesis

Shaw and Wolfe[6] have defined glucose kinetics in a group of

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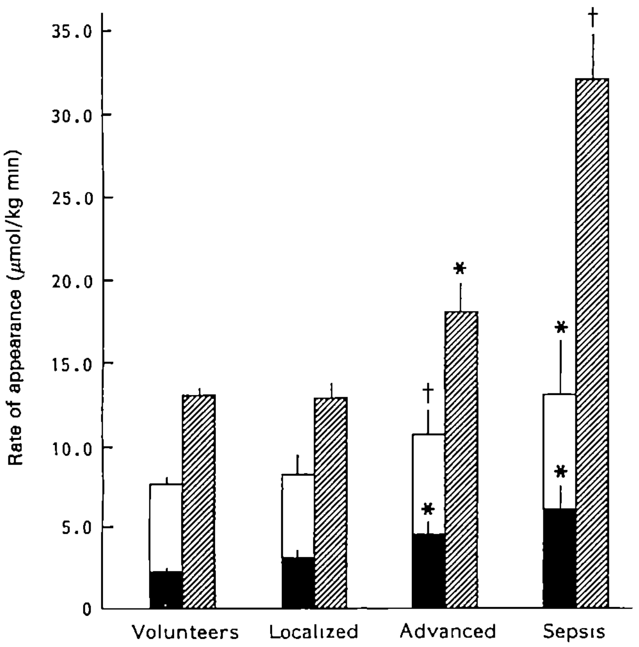

Figure 1 *The influence of localized or non-weight-losing cancer, advanced or weight-losing cancer, and sepsis on the rate of production of glycerol* (■), *free fatty acids* (□), *and glucose* (■) *compared with rates in healthy volunteers.* $^*P<0.01$, $^\dagger P<0.05$. (*Modified from Shaw and Wolfe*[7,34])

patients with early (limited to the gut wall) and advanced gastrointestinal malignancies Whereas the rate of glucose turnover in the group of patients with early lesions was indistinguishable from that seen in normal volunteers, glucose production was significantly increased in patients with advanced lesions. Similarly, tumour histology has also been demonstrated to influence the extent of increase of glucose production. The glucose turnover rates in sarcoma[22] and leukaemia[23] patients have been reported to be respectively two and nearly three times the value determined in normal volunteers, whereas the glucose turnover rate in lymphoma patients does not differ significantly from normal[23]. Other researchers have studied the effect of weight loss on glucose turnover. Holroyde *et al.* have reported that weight-stable cancer patients have rates of glucose production similar to those of normal volunteers. However, those with progressive weight loss have markedly elevated rates[37] This is a particularly significant finding as progressive weight loss secondary to uncomplicated starvation is attended by a reduction in glucose turnover[38].

The hepatic production of glucose becomes less sensitive to the usual homeostatic regulating mechanisms in some patients with cancer. If a normal volunteer is infused with glucose at a rate of 4 mg kg^{-1} h^{-1} (the dose of a typical total parenteral nutrition regimen) the suppression of endogenous glucose production will approach 100 per cent[39]. In patients with advanced gastrointestinal cancer, there is a 70 per cent reduction in endogenous glucose production[6], whereas in sarcoma and leukaemia patients hepatic glucose production is reduced by less than one-third[22–23]

The cause of elevated hepatic gluconeogenesis and its reduced suppressibility in patients with malignant tumours is unclear. The plasma levels of the hormones involved in glucose homeostasis (insulin, cortisol, growth hormone) are not consistently deranged in cancer patients[36] and are unlikely to play a significant role, although insulin receptor insensitivity would be consistent with increased gluconeogenesis The increased availability of the gluconeogenic substrates lactate, alanine and glycerol presents a plausible mechanism and, of these, lactate is probably the most quantitatively important. More than 50 years ago, Warburn described the dependence of malignant cells on anaerobic glycolysis and the resultant release of lactate[40]. Indeed, lactic acidosis has been reported in some cancer patients, particularly in those with disseminated haematological malignancy[41], and a greater rate of hepatic synthesis of glucose from lactate has been reported by several research groups[31,32]. Increased gluconeogenesis from alanine[42,43] has been described in cancer patients, which would act to accelerate wasting of body protein and which will be discussed in greater detail in a subsequent section The contribution of glycerol toward encouraging gluconeogenesis is likely to be minor[32]. The balance of available evidence suggests that the increased rate of gluconeogenesis is substrate led; however the isolation of induced gluconeogenic enzymes from hepatocytes of cancer-bearing laboratory animals[44,45] suggests that this may not be exclusively so.

Cori cycling

In the Cori cycle[46], lactate released as a result of glycolysis in peripheral tissues is used as a gluconeogenic substrate by the liver. This process consumes energy, as six ATP (adenosine triphosphate) molecules are required for the resynthesis of glucose from lactate whereas only two are produced by the glycolytic degradation of each glucose molecule. When the anaerobic glycolysis occurs in malignant tissue, the energy cost to the host is compounded by the loss of glucose parasitized by the tumour[47] Accordingly, there has been considerable interest in determining the extent of Cori cycling in cancer patients as it may be one of the fundamental metabolic changes causing cancer cachexia.

The rate of Cori cycling can be easily measured using ^{14}C- and 6^3H-labelled glucose tracers[48]. Increased rates of cycling have been measured by Holroyde *et al.*[49] in a group of 20 patients with metastatic colorectal cancer when compared with control subjects of comparable age and sex. It was inferred that tumour glycolysis was responsible for the excess lactate production, although this supposition was not confirmed by the lack of correlation between the extent of tumour burden and the increased rate of Cori cycling. Evidence for the cancer *per se* being responsible for increasing the rate of Cori cycling has been provided by the study of Eden *et al.*[50], who compared the rate of Cori cycling in patients with cancer cachexia with a control group of patients who had suffered a similar degree of weight loss but from benign causes. The rate of Cori cycling in both the fasted and enterally fed states was significantly higher in the patients with malignant disease, suggesting that it was the cancer *per se* that was responsible for this increase. However, Burt *et al.*[51] have measured an increased rate of release of lactate from the forearm of a small group of patients with localized carcinoma of the oesophagus, implying that the tumour is capable of effecting a distant influence on the metabolism of carbohydrate in host tissue. It is likely, although still conjectural, that increases in both tumour and host tissue glycolysis are responsible for the observed changes in whole body lactate metabolism.

The role played by such futile cycles in the pathogenesis of cancer cachexia has been the subject of much debate. Gold has performed considerable work in this field and describes the 'fundamental position of tumour glycolysis–host gluconeogenesis in the production of cancer cachexia'[52]. The rate of Cori cycling has been measured by Holroyde *et al*[37] in two groups of cancer patients, one with progressive weight loss and the other with stable weight. The rate of Cori cycling was considerably elevated in the first group but normal in the second, suggesting that the energy lost by the futile cycling was responsible for the weight loss However, such findings have not been universally reproduced: Kokal *et al* were unable to demonstrate any significant differences in glucose cycling rates as a function of pre-illness weight loss[35].

Eden *et al.*, having demonstrated an increase in glucose turnover and glucose cycling in cancer patients, estimated the potential energy cost to the cancer patient[51]. They calculated that, if the incomplete oxidation of glucose were to be substituted by the complete oxidation of fat, this would lead to an increase in energy expenditure of 250–300 kcal/day and a loss of 0.9 kg fat/month. However, a contrary argument has been forwarded by Young[53], who estimated that if only 15 per cent of the total lactate production is oxidized completely and 85 per cent is converted to glucose then 'there will be maintenance of high energy phosphate balance... and it is difficult to accept therefore that changes in Cori cycle activity are a significant cause of the marked body wasting in patients with progressive neoplasia'. These conflicting but equally well considered viewpoints underscore the great difficulty in accurately determining a long-term energy balance in cancer patients and, accordingly, the influence that changes in metabolic efficiency have on that balance. Nevertheless, the accelerated activity of energy wasting cycles is likely to play some role in the development of cancer cachexia.

Insulin and glucose uptake

Impaired glucose tolerance in patients with leukaemia, lymphoma and a variety of epithelial tumours was described in the 1950s by Marks and Bishop[54] and resistance to both exogenous and endogenous insulin has been subsequently demonstrated in cancer patients[55]. The insulin binding receptors of monocytes extracted from cancer patients are normal, implying that the defect is postreceptor in site[56]. Jasani *et al.* have reported a decrease in the sensitivity of pancreatic β cells to insulinogenic stimuli[57], while others have determined that reductions in both peripheral sensitivity and pancreatic release are responsible for the observed glucose intolerance[58]. However, the cause of the glucose intolerance in the setting of malignancy has undergone some critical reappraisal in recent years, and it has been suggested that it may be due to intercurrent factors such as weight loss, bed rest and sepsis rather than to the cancer *per se*[36,37].

For the plasma glucose concentration to remain constant, the increase in glucose production observed in some cancer patients must be attended by an equal increase in the rate of clearance of glucose from the plasma compartment. This occurs despite the prevailing state of insulin resistance. Results obtained from animal tumour models have suggested that the tumour acts as a 'glucose trap', consuming large quantities of glucose in the process of anaerobic glycolysis[59]. The high tumour–host weight ratio in such models (sometimes exceeding 40 per cent) casts a shadow on their applicability to patients; human tumours rarely exceed 5 per cent of body weight and therefore only very substantial metabolic changes within the tumour itself would be detectable at the whole body level. However, the glucose trap concept is supported by the demonstration of increased glucose uptake across soft tissue sarcoma-bearing limbs compared with the opposite non-tumour-bearing limb[60]. Interestingly, the forearm glucose uptake in patients with oesophageal cancer has been found to be significantly greater than in healthy controls by Burt *et al.*[51]. The plasma insulin levels were lower in the cancer patients so it is unlikely that this hormone mediated the observed changes. The authors speculate that increased non-suppressible insulin like activity (NSILA) may be responsible. NSILA is the likely cause of the hypoglycaemia seen with some non-islet cell tumours in humans[61], and is probably elaborated by the tumour itself[62]. The wider role of tumour-related NSILA remains a matter of conjecture.

Glucose oxidation

Although several studies have reported modest increases in the rate of glucose oxidation in cancer patients[19,37,63], the increases are not commensurate with the greater glucose availability, which implies a reduction in efficiency of the oxidative process[6]. In skeletal muscle isolated from patients with cancer, the activities of enzymes regulating oxidative metabolism have been found to be reduced[64], which is consistent with data gathered from studies of whole body glucose oxidation. It is likely that, in cancer patients in whom glucose production is occurring at an accelerated rate, the extra glucose production is being consumed in Cori cycling[38].

Fat metabolism

In many cases of cancer cachexia the greater proportion of weight loss is caused by depletion of body fat[18,65,66]. Loss of body fat with malignant disease has been confirmed by a variety of anthropometric techniques[14,67,68], and muscle biopsy samples from patients with cancer have been found to have only half the amount of fat present in normal controls[69]. Although the consumption of fat reserves in cancer patients is partly a reflection of reduced caloric intake, several changes in lipid metabolism have been described which probably result from cancer bearing itself, and these will be discussed in the following paragraphs. Fat metabolism in cancer patients has been the subject of far less research effort than carbohydrate metabolism, and correspondingly fewer conclusions can be drawn.

Fat mobilization

Triglyceride in adipocytes, which represents the major storage form of fat, is mobilized by hydrolysis to glycerol and free fatty acids which are released into the plasma. Using stable isotopic tracers Shaw and Wolfe[7] have measured the turnover rates of glycerol and free fatty acids in weight-stable and weight-losing patients with gastrointestinal malignancies and compared these with rates in normal volunteers (*Figure 1*). There were no significant differences in whole body glycerol and fatty acid kinetics between the weight-stable patients and the normal volunteers, but those with weight loss had significantly elevated rates of release into the plasma of both glycerol and free fatty acids. These data, which are in agreement with the work of others[15,70], suggest that the loss of fat reserves seen in patients with cancer cachexia results from increased fat mobilization rather than decreased synthesis. However, definitive studies of the influence of cancer on lipogenesis in human subjects have not been performed, so it is possible that both mechanisms are operating to reduce body fat stores.

Lipid clearance

Lipoprotein lipase is the enzyme responsible for the clearance of triglyceride molecules from the plasma. Although hyperlipidaemia is not a marked finding in cancer patients, it has been found in association with some tumours[71], and the proposed mechanism is a reduction in activity of this enzyme. Support for this hypothesis has recently been provided by Vlassara *et al.*[72] who found that the plasma lipoprotein activity in a group of cancer patients was reduced and that there was a correlation between weight loss and the extent of reduction of enzyme activity. The decreased lipoprotein lipase activity that occurs in uncomplicated starvation is mediated by a reduction in the plasma level of insulin. However, the insulin levels in the patients in Vlassara's study were normal, suggesting that this was not the mechanism responsible for the observed changes.

Fat oxidation

There is a considerable body of data to suggest that fat is oxidized at an increased rate in cancer patients[14,15,50,63,74], although as is common in studies involving small numbers of patients with heterogeneous conditions this finding is not universal[75]. Fat oxidation rates determined in a series of 70 patients with colorectal or gastric cancer by a combination of indirect calorimetry and urinary nitrogen excretion have been recently reported by Hansell *et al.*[19]. They found that the patients with cancer had significantly higher fat oxidation rates (and significantly lower carbohydrate oxidation rates) than control patients with benign disease. Patients with cancer and weight loss oxidized fat more rapidly than either patients with cancer and no weight loss or patients with weight loss caused by benign disease. Similarly, patients with hepatic metastases had a significantly greater fat oxidation rate than patients with localized malignant disease. Others have reported that in cancer patients a greater percentage of the body's energy requirements is provided by fat than in normal volunteers, and that fat is mobilized and oxidized with at least the same efficiency as in health[15]. It is unlikely that malignant tissue *per se* is responsible for the increased fat oxidation, but rather that the changes induced in the regulation of metabolic pathways occurring in normal host tissues in the cancer-bearing state favour fat oxidation.

Protein metabolism

Loss of body protein in patients with cancer cachexia is manifested clinically as skeletal muscle atrophy and hypoalbuminaemia, and is associated with an impaired tolerance of treatment procedures[2]. Significant protein loss may occur in patients who are maintaining what would be in health an adequate intake of nitrogen and calories, implying that tumour bearing *per se* is able to exert a detrimental influence on whole body nitrogen balance. However, a negative nitrogen balance is not an inevitable accompaniment of malignancy. Nearly 30 years ago, Watkin[76] measured nitrogen balance in a large group of cancer patients and found a range of responses from positive to very negative balances, and he thoughtfully related the more negative nitrogen balances with increased disease 'activity' (reflecting weight loss, increased resting energy expenditure and other factors). This concept concurs with our own observations, in which patients with aggressive metastatic disease[77] or those with histological tumour types frequently associated with a poor prognosis (e.g. sarcoma[22]) tend to lose protein significantly more rapidly than those with less aggressive disease.

Whole body protein kinetics

The rate of whole body protein turnover can be measured using isotopically labelled amino acids as metabolic tracers, and a number of such studies in cancer patients have produced a spectrum of results. A consistent 50–70 per cent increase in turnover rates in large groups of patients with lung and colorectal cancer has been reported[20] and there have been similar findings in patients with small cell cancer[78] and in children with leukaemia[79,80]. Norton *et al.*[81] found an inconsistent response in a diverse group of cancer patients, whereas others have found no difference between patients with cancer and age-matched normal controls[82]. Several investigators have suggested that whole body protein turnover is increased with advancing stage of disease and weight loss[78,83–85].

This accelerated protein turnover seen in many cancer patients contrasts with the reduction in total protein turnover observed in cases of simple starvation[86]. Recently, to distinguish the metabolic effect of pure malnutrition from those of cancer bearing, Jeevanandam *et al.* compared the protein kinetics of malnourished cancer patients with those of patients who were equally malnourished as a result of benign disease and with those of a group of starved normal subjects[87]. Compared with the non-cancer patients and starved normal subjects, whole body protein turnover in the cancer patients was elevated by 32 and 35 per cent respectively. These results confirm the observations made by Brennan nearly a decade earlier that in cancer cachexia there is a maladaptation to the starved state, with a continued mobilization of protein and calorie reserves in the face of a reduced intake[5]. An example of this is the decreased efficiency with which simple substrates limit the rate of gluconeogenesis and protein flux in patients with advanced cancer[31,73,88].

Protein turnover is an energy expensive process which accounts for 10–20 per cent of basal metabolic expenditure[89] The reduction in protein turnover seen in simple starvation accordingly represents an adaptive response[90], and it has been suggested that its failure to occur in some cases of malignancy is responsible for the development of cancer cachexia[91]. This hypothesis has recently been examined in substantial groups of cancer patients and normal controls[20] and, although the cancer patients had a significantly higher rate of protein turnover, their resting metabolic expenditure was not increased nor was there any correlation between individual rates of protein turnover and energy expenditure. These results suggest that when protein turnover is increased in cancer patients it is unlikely to play a major role in the development of cancer cachexia.

The influence of the cancer *per se* on whole body protein metabolism has been a matter for some conjecture. The concept of the tumour having a 'nitrogen trap' which parasitizes amino acids from healthy tissues was developed by researchers working with rapidly growing transplantable animal tumour models[92,93], but it is unlikely to be applicable to patients in whom tumour bulk is usually a much smaller percentage of body weight. It is more plausible that the tumour is releasing a humoral agent or agents which effect the observed metabolic changes. Glass *et al.*[94] attempted to quantify the influence of tumour bearing on protein dynamics by studying a group of patients with colorectal carcinomas just before and 12 weeks after resection. They were unable to demonstrate a significant difference in whole body protein metabolism after tumour excision, and concluded that the primary tumour does not alter protein kinetics. However, the study group comprised patients with localized lesions whose nitrogen flux was comparable to that of normal controls, and so it is perhaps not surprising that tumour excision caused no change.

Skeletal muscle metabolism

Whole body protein turnover studies reflect the sum total of synthesis and degradation rates in the individual tissues. Accordingly, it is possible for synthesis and/or catabolism to be reduced in one particular tissue while whole body turnover is increased[95]. Several investigators have attempted to determine the manner in which the protein kinetics of individual tissues are affected by cancer Lundholm *et al.* used the rate of incorporation of [^{14}C]leucine by skeletal muscle biopsies incubated *in vitro* to compare synthesis rates in a heterogeneous group of 43 cancer patients with 55 age- and sex-matched controls[96]. They found that the capacity of the muscle fibres removed from the cancer patients to incorporate the amino acid tracer was significantly impaired, and that having been incorporated the rate of loss of tracer was also greater in the cancer patients. The group concluded that malignant tumours provoke a decrease in protein synthesis and an increase in protein degradation. In a subsequent series of experiments the same group used arteriovenous differences in levels of 3-methylhistidine, an amino acid which is relatively specific to skeletal muscle, and found that there was no significant difference in the rate of appearance of this marker in patients with cancer and controls who were depleted with benign disease[97] They concluded that the effect of malignant tissue was to reduce the rate of protein synthesis. As skeletal muscle comprises the majority of the body's protein, changes in skeletal muscle protein kinetics are subsequently likely to be manifested at the whole body level. The results of Lundholm's group are therefore at odds with a substantial body of whole body kinetic data which suggests that whole body protein synthesis is either unchanged or increased[20,78–80,83,84]. Recently, Shaw and colleagues have determined *in vivo* fractional synthesis rates (FSR) of muscle in patients with benign disease, weight-stable patients with malignant disease, and patients with cancer cachexia[85]. There were no significant differences in the rate of muscle FSR between patients with benign disease and weight-stable cancer patients, but there was a significant increase in FSR in those patients with cancer cachexia. Given that these patients had lost weight (and presumably protein), this implies the occurrence of an even greater increase in the rate of degradation of muscle protein, and indeed increased activities of lysozymal enzymes isolated from skeletal muscle of cancer patients have been reported[64,96]

Hepatic protein synthesis

There is a paucity of data on the rate of hepatic protein synthesis and catabolism in cancer patients. Using the same *in vitro* methodology employed in their study of skeletal muscle metabolism, Lundholm *et al* have reported an increase in the rate of protein synthesis in liver biopsies from cancer patients[64]. These results are consistent with those from our own laboratory, in which we have demonstrated *in vivo* a significant increase in the fractional synthetic rate of protein of hepatic tissue in patients with cancer cachexia, but no difference between the hepatic FSR of weight-stable cancer patients and patients with benign disease[85]. There are no data describing the rate of catabolism of structural hepatic proteins in cancer-bearing patients. However, a recent report in which organ imaging techniques were used to determine liver size in a small number of patients with cancer cachexia suggested that there was relative sparing of visceral protein[98], which implies that the observed increase in hepatic protein synthesis is likely to be attended by an equal increase in protein catabolism

Many patients with advanced malignancy are hypoalbuminaemic, which may result from a reduced rate of synthesis, an increased rate of breakdown or a loss of albumin from the intravascular volume. As albumin degradation rates have been demonstrated to be normal in cancer patients[99,100] and with the exception of cases of malignant effusion the distribution of albumin is relatively unchanged, this implies that the rate of synthesis is decreased. However, this is contrary to some recent data from our laboratory in which we measured the rate of synthesis of albumin using a [^{14}C]leucine marker[101]. A significantly higher rate of albumin synthesis was found in those patients with cancer cachexia compared with rates in cancer patients who were weight stable, and in patients with benign disease. It is clear that the influence of malignancy on hepatic structural and secretory protein synthesis has yet to be clearly resolved.

Treatment of cancer cachexia

Nutritional support

Following the introduction of safe total parenteral nutrition (TPN) techniques nearly 20 years ago, it was hoped that the great majority of cachectic cancer patients could be repleted before surgical treatment, radiotherapy or chemotherapy, and that a reduction in treatment morbidity would be effected. The enthusiasm of the initial reports describing the efficacy of TPN in cancer patients[102] has not always been reaffirmed[103]. It has become clear that providing sufficient nitrogen and calories to a patient with cancer cachexia does not augment lean body mass as efficiently as can be achieved in a malnourished patient with benign disease. The use of TPN in cancer patients raises several questions, such as whether hyperalimentation promotes growth in malignant tissue, how the TPN prescription can be tailored to ameliorate the metabolic defects associated with cancer, and whether the provision of TPN leads to an improved patient outcome.

The concern of clinicians that the protein and energy substrates provided by TPN will be consumed preferentially by the tumour has some support from the results of experiments performed with animal tumour models, in which tumour growth is encouraged more than repletion of host tissues[104–106]. However, to date, stimulation of tumour growth by TPN has not been observed in patients[107]. The most elegant evidence that TPN does not have a deleterious effect has been provided by Mullen *et al.*[108] who used the *in vivo* rate of incorporation of [^{15}N]glycine as a measure of protein synthesis. They found that the tumours of patients who were given TPN for 7–10 days before surgery were synthesizing protein no more rapidly than the tumours of the control patients who were on an *ad libitum* oral diet. Although some caution must be exercised in the interpretation of these results as a net increase in tumour size may have resulted from a reduction in the rate of protein catabolism, it is most likely that malignant tissue is synthesizing protein at a maximal rate and that its rate of growth cannot be significantly affected by the provision of extra nutrients[109].

It is generally agreed that approximately 130 per cent of the RME needs to be provided to cancer patients[110], but there are few data that clearly indicate which is the optimal caloric source Despite some cancer patients having marked changes in intermediate metabolism, they have been shown to be able to oxidize efficiently both infused glucose and fat[111]. There is some evidence from a laboratory tumour model that the provision of calories as fat retards tumour growth[112], but this has not been duplicated in other animal models[113] and there is no evidence from human studies to support these findings. Shaw and Holdaway have demonstrated that infusion of isocaloric volumes of glucose and fat (administered as Intralipid 20, KabiVitrum Laboratories, Stockholm, Sweden) have an equal ability to spare protein at the whole body level, although lipid infusion fails to suppress endogenous glucose production[114]. Infused glucose is able to suppress gluconeogenesis in cancer patients[42], but it does not do so with the same efficiency as in healthy volunteers[6].

Although it is possible to restore the weight of a cachectic cancer patient with parenteral nutrition, it has been questioned whether the weight gain is primarily as fat[115] or whether it represents a useful replenishment of the lean body mass. There are several reports of positive nitrogen balances being achieved in cancer patients on TPN[43,116], but these studies require meticulous sample collection and may be difficult to interpret in the presence of a growing tumour. However, longitudinal studies of body composition over a 1 month course of TPN have shown no increase in total body nitrogen, despite increases in body fat and total body potassium[10]. These data are compatible with the results of isotopic studies, which have demonstrated an attainment of nitrogen equilibrium with TPN, but not the protein anabolism which is readily achievable in patients depleted by benign disease[117] (*Figure 2*). There is evidence to suggest that leucine is central in the regulation of protein metabolism[118], and leucine-enriched TPN has been provided to cachectic cancer patients in an attempt to improve the nitrogen balance[119,120], with a small improvement in nitrogen balance being demonstrated.

It is likely that the difficulty in achieving restoration of lean body mass with TPN in cachectic cancer patients is partly responsible for the paucity of convincing evidence of its therapeutic efficacy[103]. Prospective randomized trials of less than 1 week of TPN have failed to demonstrate any advantage to the study group over the control group fed *ad libitum*[121,122]. A recently published analysis of the pooled results of 18

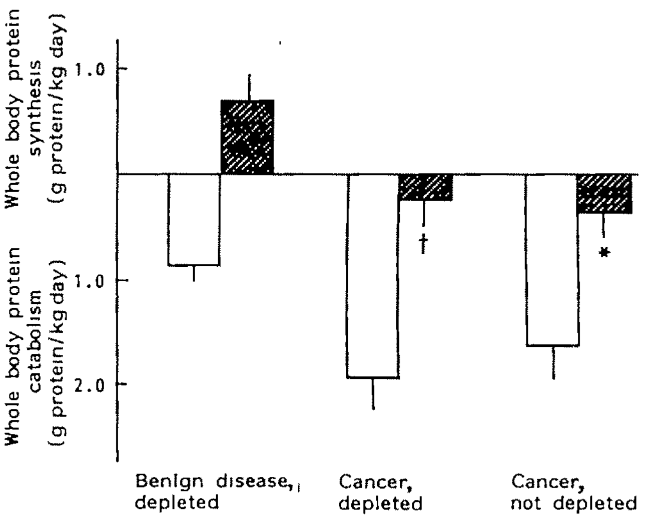

Figure 2 *Response to total parenteral nutrition* (■) *of depleted patients with benign disease, cancer patients with depletion and cancer patients without depletion compared with basal values* (□). $^*P<0.01$, $^†P<0.05$. (*Modified from Shaw*[117])

randomized trials assessing the effectiveness of perioperative TPN (16 of which consisted of cancer patients) concluded that there was little evidence supporting the routine use of perioperative TPN, but that it may have a role in supporting a subgroup of patients who are at high risk[123]. The authors of this paper were generally critical of the methodology of the trials performed to date, and comment that the effectiveness of TPN may have been underestimated by inclusion of patients who were not malnourished. Certainly, some trials have demonstrated advantages to the patient who received TPN: Heatley *et al.* followed the postoperative course of 70 patients with gastric cancer who were randomized to receive either TPN for 7–10 days or a normal diet, and reported a significant reduction in the occurrence of wound infection in the group who received TPN[124]. A preoperative course of TPN of a similar length in a group of patients with gastrointestinal malignancies reduced the incidence of complications from 19 per cent in the control group to 11 per cent in the treatment group, and the mortality from 11 to 3 per cent[125]. However, any advantage attributed to TPN must be weighed against the risks of pneumothorax and catheter-related septicaemia.

Pharmacological manipulation

As the provision of adequate calories and nitrogen does not ensure protein accretion in cachectic cancer patients, there have been several attempts to counter adverse tumour-associated metabolic changes by administration of pharmacological agents. An example is a trial involving 101 intensively pretreated cancer patients who were randomly assigned to receive either hydrazine sulphate, which inhibits a key enzyme in the gluconeogenic pathway, or a placebo[126]. The treatment group experienced significantly improved weight stabilization and glucose tolerance. Megestrol acetate, an anabolic steroid, has been recently reported to produce enhanced appetite and increased weight in a group of 28 patients with breast cancer[127]. Nearly a decade ago Schein *et al* [128] argued lucidly that many of the cancer-related metabolic derangements were a result of insulin resistance and suggested that many of these could be ameliorated by the provision of exogenous insulin. This proposal has been supported by the results obtained from animal model experimentation[129–131] but to date no human studies have been published.

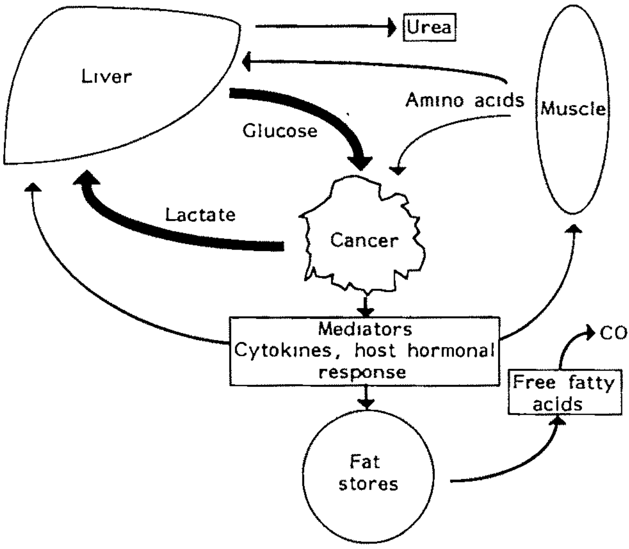

Figure 3 *Overview of the proposed metabolic changes associated with advanced cancer*

Although these and other trials involving anticachectic agents have shed some light on the mechanisms of cancer cachexia, no agent has yet been demonstrated meaningfully to improve the clinical course of cancer patients.

Mediators of the metabolic response to cancer

It was long held that the metabolic changes observed in cancer patients at the whole body level were a reflection of the metabolic activity of the malignant tissue *per se*. From this supposition was born the concept of the tumour acting as an internal parasite, trapping nitrogen and energy substrates as the host tissues became progressively more malnourished[132]. Despite the alluring simplicity of this hypothesis it fails to account for the profound metabolic changes that have been documented in some patients with apparently trivial tumour burdens[133], nor does it explain the changes in metabolism detected in host tissue distant from the tumour site[51].

An alternative theory advanced to explain these observations is that tumours release small molecular weight proteins which alter the activities of various host enzymes[30] (*Figure 3*). A large number of polypeptides and other substances secreted by tumour cells have been described, such as toxohormone[134] and lipid mobilizing factor[135], to which have been attributed various roles in the causation of cancer cachexia, largely on the basis of animal experiments. However, there is little evidence that convincingly relates these substances to the metabolic changes seen in cancer patients.

The similarities between the metabolic responses to sepsis and trauma to that provoked by tumours have been clearly described by Brennan[5] The loss of nitrogen and increased turnover of glucose and mobilization of fat which occur in

Table 1 *Metabolic changes commonly associated with advanced or weight-losing cancer, severe sepsis or multiple trauma, and depletion due to benign disease (or in some cases starvation in normal volunteers)*

	Cancer	Sepsis/trauma	Starvation	Reference
Carbohydrates				
Gluconeogenesis	↑	↑	↓	6, 31, 32, 37, 38, 141, 142
Glucose recycling	↑	↑	–	22, 49, 50, 141, 142
Insulin resistance	↑	↑	–	55, 58, 143
Fat				
Lipolysis	↑	↑	↑	7, 15, 144, 145
Fat oxidation	↑	↑	↑	14, 15, 19, 145, 146
Protein				
Whole body flux	↑	↑	↓	20, 77, 89, 141, 142, 147
Net catabolism (NPC)	↑	↑	↑	6, 22, 141, 142
Responsiveness of NPC to total parenteral nutrition	↓	↓	↑	116, 117
Energy				
Resting metabolic expenditure	↓/N*/↑	↑	↓	13, 16, 18, 21, 25, 26, 27, 146, 148

*No change

severely septic or injured patients result from the combined influences of counter-regulatory hormone secretion and the release of inflammatory mediators from cells of the immune system[136]. It has been suggested that similar mediators released by immunocytes in response to tumour cells are responsible for the metabolic response to cancer. Cachectin, a 17 kDa polypeptide released by macrophages which acts as a mediator of endotoxic shock[137], has recently been found to share strong sequence homology with tumour necrosis factor (TNF)[138], also a macrophage product. It may be that cachectin/TNF is central to the mediation of the metabolic response to both sepsis and cancer[139]. Recently, Wilmore and coworkers have reported a negative nitrogen balance in cancer patients infused over a 5-day period with recombinant TNF, which they attributed to the anorexia induced by the TNF rather than to a cytokine-specific effect on protein metabolism[140] Kern and Norton have proposed a mechanism explaining the metabolic derangements of cancer cachexia in which the tumour stimulates the host's immune cells to secrete factors such as cachectin/TNF whose primary role is cytotoxic, but which have secondary metabolic effects[8].

Summary

Malignant tumours do not have a consistent effect on the intermediary metabolism of the host However, patients with advanced disease and/or those demonstrating cancer-related cachexia typically have accelerated rates of energy substrate and protein turnover despite reduced calorie and nitrogen intake. In this manner the metabolic response to cancer cachexia is opposite to that seen in uncomplicated starvation, but rather bears many similarities to the changes described in patients with sepsis and trauma. The rates of gluconeogenesis and Cori cycling, fat mobilization and oxidation, and protein synthesis and degradation tend to be increased, and there is greater difficulty in replenishing lean body mass with methods of nutritional support (*Table 1*). The metabolic response to cancer may be largely effected by mediators released by cells of the immune system, but this matter remains conjectural. Beyond the provision of adequate calories and nitrogen, and removal of malignant tissue, there are presently no metabolic therapies available which have been demonstrated to influence clinical outcome.

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Xanthogranulomatous cholecystitis

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This short review discusses the incidence, cause and methods of diagnosis of xanthogranulomatous cholecystitis. The association between the condition and gallbladder cancer is also considered.

Keywords: Cholecystitis, gallbladder

When lipid in the bile enters the mucosa of the gallbladder, it may be taken up by macrophages to give the familiar lesion of cholesterolosis or, if limited to a small area, the equally innocent cholesterol polyp. In contrast, when lipid and accompanying bile pigments penetrate into the connective tissue of the wall, the resulting inflammatory process, in which macrophages again predominate, is potentially much more serious. The lipid is sometimes oxidized to a coloured chromolipid, and the condition has thus attracted such labels as ceroid granuloma[1] or ceroid-like histiocytic granuloma[2]. More recently, these terms, together with other labels such as fibroxanthogranulomatous inflammation[3] and biliary granulomatous cholecystitis[4], have been abandoned in favour of xanthogranulomatous cholecystitis[5], a descriptive term first used by McCoy *et al.*[6].

Xanthogranulomatous cholecystitis is seen in a small but significant proportion of routine cholecystectomy specimens, ranging from 0·7 per cent in Illinois[7] to 1·8 per cent in Sheffield[8]; an intermediate incidence of 1·2 per cent was noted in Japan[2]. A more recent report from Japan[9] claims an incidence of 9·0 per cent, but it is based on a smaller series of cholecystectomies, and may therefore not be representative. In the Sheffield series, xanthogranulomatous cholecystitis was more common than gallbladder carcinoma, even though it remains unfamiliar to many general surgeons and histopathologists.

Some authors have assumed that xanthogranulomatous cholecystitis is simply a variant of conventional chronic cholecystitis[1,5,7,10], differing only in intensity[11]. Histological evidence of ordinary chronic inflammation is generally seen[8], and gallstones are present in a large majority of cases[2,5,7]. However, others have emphasized an association with a recent attack of acute cholecystitis on a background of chronic cholecystitis and chronic cholelithiasis[8]. Aschoff–Rokitansky sinuses are often found in association with foci of xanthogranulomatous cholecystitis[2,5,8,11], and ulceration of the surface mucosa is also common[8]. It has therefore been suggested that xanthogranulomatous cholecystitis is initiated by a combination of acute inflammation and obstruction. Bile then enters the stroma through an ulcer of the surface mucosa, or through ruptured Aschoff–Rokitansky sinuses[8,11]. Macrophages are attracted to the site of inflammation, and ingest the lipid to form large round pale xanthoma cells. As the inflammatory process undergoes organization, some of the cells become elongated to the other typical configuration, which is that of an elongated spindle[8] Giant cells of foreign body or Touton type are also seen. This hypothetical sequence derives support from experimental observations on the prototype of xanthogranulomatous inflammation, xanthogranulomatous pyelonephritis[12]. Similar conditions are said to occur in a number of other organs, including lymph node, bone, lung, soft tissue, vermiform appendix, vagina, endometrium, fallopian tube and ovary[13].

The symptoms associated with xanthogranulomatous cholecystitis are usually those of acute or chronic cholecystitis[7,8,11], but some patients have presented with anorexia, pain and a right hypochondrial mass[14], suggesting a diagnosis of gallbladder carcinoma. Similar misdiagnosis may happen on organ imaging; for example, ultrasonography may show diffuse or nodular thickening of the gallbladder wall which may be misinterpreted as tumour[8,14–16] or intramural abscess[17]. Equally misleading results may be obtained with computed tomographic scans[9,14,18] and angiography[9]. Oral or intravenous cholangiograms usually fail to outline the gallbladder.

At operation, there are frequently prolific adhesions to other organs, with extension of the yellow masses of xanthogranulomatous inflammation to structures such as the liver, small and large intestine, and omentum[8]. The gallbladder may perforate[19], and fistulae extending to the skin and duodenum have been described[8]. The gallbladder itself may be sufficiently irregular to suggest the diagnosis of carcinoma, and the surgeon may feel obliged to request urgent frozen section examination[8]. Finally, the histological appearance of large pale cells interspersed with elongated spindle cells has been mistaken for both carcinoma[5] and sarcoma[3], though familiarity with the lesion should be sufficient to prevent misdiagnosis at this stage.

Not only can xanthogranulomatous cholecystitis imitate carcinoma in various ways, but there appears to be a positive association between the two lesions. For instance, gallbladder carcinoma was over-represented in a series of patients with xanthogranulomatous cholecystitis seen in Sheffield[20], and the condition was seen more frequently than expected in a series of gallbladder carcinomas studied in Manchester[21]. The reason for this association is not clear It may simply be that xanthogranulomatous cholecystitis and adenocarcinoma are both complications of cholelithiasis and cholecystitis of particular duration or degree, or it could be that tissue disruption by carcinoma facilitates the entry of bile into the stroma[21]. The association is important because. when both lesions are present in the same specimen, there is a possibility of overlooking the carcinoma altogether[22], or there is a risk of over- or underestimating the extent of tumour and arriving at an incorrect estimate of prognosis.

Xanthogranulomatous cholecystitis is a diagnosis which is usually made only after cholecystectomy has been completed, so that a discussion of the correct treatment is largely superfluous However, cholecystectomy remains appropriate in the few cases where intraoperative diagnosis is made by frozen section, particularly because of the association with gallbladder carcinoma. Unfortunately, there may be a high risk of postoperative wound infections and other septic complications[8].

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Announcement

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Strength of the colon wall in diverticular disease

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Studies of the aetiology of diverticular disease of the colon have been focused on intraluminal pressure for almost three decades. It is only relatively recently that the mechanical properties of the wall of the colon have been examined. The tensile strength and elasticity of the colon decline with age and this is most marked in the left colon which is the narrowest and thickest part. This review discusses the case that the mechanical properties of the bowel wall are key factors in the development of diverticular disease. The potential role of high fibre diets in reducing the pressure changes which may stress the colon wall in this disease is also considered.

Keywords: Colonic wall, pressure, collagen, fibre, diverticula

Current ideas on the aetiology of diverticular disease focus on the role of intraluminal pressure and only recently has the strength of the colon wall been implicated. The mechanical properties of most tissues change with age and diverticular disease of the colon is particularly common towards the end of life To most surgeons, the hallmark of diverticular disease is, apart from the diverticulum, a sigmoid colon with a thick muscle coat. But, as is well known to most surgeons, diverticula also arise along the entire length of a thin, atrophic colon which suggests that a raised intraluminal pressure is not a *sine qua non*. Further evidence suggests that there are no additional smooth muscle cells in the wall of the bowel in diverticular disease and that the thickened muscle is often the result of the taeniae coli contracting and bunching the sigmoid colon together so that its thick muscle encroaches on the lumen.

This review argues the case for considering the mechanical properties of the bowel wall as important in withstanding the 'wear and tear' of any pressure changes that affect it, secondary to the narrowing of the lumen, and sees a role for high fibre diets in minimizing or avoiding these changes.

Colonic muscle and the pressure theory of diverticular disease

Diverticular disease is the most common disorder of the human colon and has an important bearing on the health of a large percentage of the elderly Western population. A common change in the wall of the colon is that its muscle coat is markedly thickened, giving rise internally to a narrow lumen, redundant mucosa apparently mildly obstructing it further[1]. The diverticula form in two rows between the mesenteric and antimesenteric taemae as mucosal extrusions outside the colonic wall. For almost the last quarter of the century since Arfwidsson and Kock[2] and Painter[3] first described raised intraluminal pressure in the sigmoid colon of patients suffering from diverticular disease, attention has been paid to pressure phenomena in the generation of the diverticula.

Motility was first shown to be greater in response to food and cholinergic stimulation in symptomatic diverticular disease[4,5] but this is not invariably so since the gastrocolic reflex elicited by food may be absent in severe symptomatic disease[6] and the motility responses are diminished when the pathological features of inflammatory damage are extreme[7]. The increased motility in diverticular disease can be reduced by myotomy and bran, both of which relieve painful symptoms[8,9], suggesting that muscle involvement, a raised pressure and symptoms are related.

Excision of the diverticular disease segment, however, does not reduce the motor activity in the remaining distal bowel[10,11], suggesting that the muscle abnormality in symptomatic diverticular disease eventually becomes widespread. Confirmation of the wide extent of involvement was provided by Trotman and Misiewicz[12] who positioned pressure sensors high in the left colon with a colonoscope and found that the pressure in the descending colon was higher there than in the more distal sigmoid colon. Others have, however, failed to find consistently raised intraluminal pressure[13,14] Trotman and Misiewicz attributed this failure in the study of Weinreich and Anderson[13] to possible displacement of the pressure sensors from the sigmoid colon into the rectum which is not affected by diverticular disease. This seems unlikely in view of the similar finding of Eastwood and his colleagues[14] who also reported a relatively low intraluminal pressure in asymptomatic patients with diverticular disease and it is conceivable that this represents an earlier stage of the disease in which pressure change is not consistently, if at all, present.

Individual constituents of the colonic wall

The predisposition of the distal colon to diverticula formation and the increasing incidence of diverticular disease with age prompted a study of the musculature of the colon by Pace[15], who showed that the colonic muscle in general increased in thickness with age and became thickest in the distal colon.

Little attention has however been paid to the other components in the colonic wall. The mucosa is extremely expansile but weak. Its ability to stretch to many times its original length enables diverticula to form as 'balloon' herniations of the relatively elastic mucosa through an otherwise contracted, thickened, inelastic colonic wall. The submucosa consists of collagen fibrils in a matrix of mucopolysaccharide ground substance. Collagen is the most important biological tissue in the colonic wall with a tensile strength of 10^9 Nm^{-2} (Reference 16), as opposed to relaxed muscle which is 10000-fold weaker with a tensile strength of 10^5 Nm^{-2} Muscle undergoing contraction can raise the tensile strength to 10^7 Nm^{-2} (Reference 17) but, at that, the strength of the muscle still lags behind that of the collagen component.

In the colonic wall the collagen is arranged in a discontinuous criss-cross network which allows for strength and expansi-

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bility[18]. The collagen fibrils are smaller in width but increase in number with age in the left colon, a trend which is significantly greater in diverticular disease[19]. Elastin fibres in the colon also increase in number but deteriorate in quality with age[15]. Whiteway and Morson[20] found no additional muscle cells but an increase of elastin in the thickened taeniae of diverticular diseased colon, the elastin being laid down in a contracted form leading in turn to progressive shortening of the taeniae coli which bunch the circular muscle together and obstruct the bowel lumen, perhaps producing at this stage the increments of pressure which result in increased stress on the bowel wall and the production of symptoms.

Biomechanics of the colon and the effect of ageing

The elastin change also shows qualitative differences, as in skin where there is a fibrillary degeneration with age, which reduces the elastic deformation characteristics of skin with age. There are similar age-related changes in the mechanical properties of the colon wall, one of which is a reduced expansibility[21,22].

Since diverticula are predominantly found in the elderly, the mechanical properties of the colonic wall might be expected to vary at different ages. Such studies have been carried out on Japanese[21] and on Scots and Ugandans[23] and confirm that the tensile strength of the colon declines throughout adult life in all racial groups and that its expansile properties diminish with age. Both studies examined the stress–strain curve to rupture of the intact colon wall in post-mortem colons. The tensile strength effectively measures the strongest structure in the wall, namely collagen.

Maintenance of form: stress and why the wall bulges

The colon, like other tissues, is under 'pre-strain'[24]. Pre-strain is the phenomenon seen in certain living tissues indicating that they are under varying amounts of stretch and this is demonstrable in the shortening of the colon or of a blood vessel which takes place when it is excised from the body. Pre-strain allows tissues to expand in one direction without unduly altering their length in the other. For example, if blood vessels were like steel then a change in diameter in the femoral artery of 0·5 mm would be associated with a change in length of 25 mm. Such a situation would be incompatible with the maintenance of form.

The maintenance of shape and form under a variety of stresses and strains is a property of what is termed viscoelasticity. Biological tissues behave both like a viscous liquid and an elastic solid at the same time. The stress–strain curve of biological tissues is non-linear, unlike metals such as steel[16,24] and reflects their composite nature as fibres of elastin and collagen embedded in a viscoelastic amorphous gel.

Skin and blood vessels are the biological tissues which have been most extensively studied. Daly and Odland[25] demonstrated alterations in the elastic deformity of skin under stress with age. The effects of age could be reproduced in younger skin by removing elastin enzymatically, suggesting that elastin degradation with age might account for the difference. In the aorta the diameter increases with age, as does the wall thickness. However, wall thickness increases more than diameter and the wall shows increasing stiffness[26]. Such age-related changes may not be peculiar to skin and blood vessels since the colon undergoes similar changes with age which may influence the development of disease in both structures. The colon is essentially a cylindrical tube and its viscoelastic nature allows its dimensions to vary with muscular contraction and distension with faeces and flatus.

The stress acting on the wall of a cylindrical structure such as the colon varies according to the intraluminal pressure, the radius and the thickness of the wall[26] being a variant of pressure = (thickness × stress)/radius which is similar to the law of Laplace, which particularly applies to spherical structures. The pressure required to distend the colon is greatest when the radius is small, as when blowing up a balloon, the balloon being hardest to distend when there is no air in it The greater the intraluminal pressure the greater the stress in the wall of the colon. Thus to allow passage of faeces and flatus, the distal colon, which is narrowest, must experience greater intraluminal pressure and greater stress in its wall. Greater stress in the wall with the passage of time leads to degenerative changes in the collagen and elastin, which could in turn predispose to development of diverticula. As diverticular disease muscle encroachment further narrows the colon[20], greater intraluminal pressure must be generated to distend and maintain its lumen which could rupture existing diverticula.

The more solid the faeces the greater the pressures required to propel them through the colon. This pressure is generated by the active forces of peristalsis, segmentation and mass contraction throughout the entire colon rather than by a central pump as in the case of the circulation. The more solid the faeces the greater the work done and the stress experienced by the colonic wall. The colon is narrowest in its distal sigmoid part and this segment becomes narrower with increasing age[23]. Thus the ageing pelvic colon is most subjected to stress. Increased stress damages the colon resulting in a loss of tensile strength and elasticity. This has been confirmed by Iwasaki[21] and Watters *et al.*[27] who found a decline in both properties with increasing age. The proximal colon was much stronger and more expansile than distal colon.

Nutritional factors

Since diverticular disease is prevalent in Western countries but not in Africa and Asia, the African colon should be stronger and more expansile than that of the European. This was shown by Watters *et al.*[23] who found that the difference was most significant in the distal colon, the area in which a Western population is more susceptible to formation of diverticula. An interesting feature of this study was that the infant African and European colon began with similar properties suggesting that the differences in adult life are environmental and not genetic. Yet if environmental factors, presumably dietary ones, are important in diverticular disease formation, there is no difference in the tensile strength of Edinburgh colons with and without diverticular disease in the over 50 age group studied[23] Perhaps by 50 years of age the Edinburgh colon population, with a lower fibre intake than the African one, might be expected to be prediverticular in status.

Collagen is the most abundant protein in mammals and helps to maintain tissue structural integrity. However, this apparently fails in the colon when exposed to the added stress of propulsions through a progressively narrowing bowel lumen. Collagen is known to have certain inter- and intramolecular cross-links which stabilize it and give mechanical strength to the tissue in which it is situated Although cross-linking increases with advancing age, the exact position of the cross-links is not known. Collagen may also change qualitatively in a number of tissues by being non-enzymatically glycosylated This increases, for example, in the collagen of the cornea of diabetes mellitus patients[28]. Diabetic patients are prone to diverticular disease at an early age suggesting that there might be a defect or an increase in the degree of glycosylation of the colonic collagen with advancing age.

There are many studies[29] showing that the raised pressures found in symptomatic diverticular disease can be kept low by fibre added to the diet[9]. The precise mechanism of action of fibre is still largely unknown. It may act, as far as the distal colon is concerned, mainly by its bulking action[9], giving rise to a wider lumen, and, by the Laplace law, leading to a lower pressure which in turn lessens the stress in the colonic wall. It would be interesting in this regard to study the stress–strain curve in European subjects who have consistently maintained a high fibre diet to determine whether their colons stay stronger like those of their African counterparts. The change from a low to a high residue diet may prevent the taenial shortening and the smooth muscle contracture of the pelvic colon.

Secondary damage

The contraction of the colon which results in a thicker wall may be to a degree a compensatory mechanism for increased stress in the wall, but could also disadvantageously compress the colonic microcirculation and restrict blood flow and tissue oxygenation[29].

Increased pressure on or in the colonic wall could also influence blood flow, especially at the time when contractions are being maximally exerted as, for example, during segmentation movements, mass contraction or abdominal straining. Reduction in blood flow could hasten the degeneration processes in the colon wall and further affect the tensile strength of the tissues predisposing to the complications of diverticular disease, necrosis, perforation or to the invasion of the colonic wall by infection.

Conclusion

It is a feature of the common form of diverticular disease in Western man that it has a late onset. We envisage its development deriving from years of under filling of the colon from low residue diets in contrast to the situation in the African where the lumen is wider with bulkier faeces and the colon wall remaining for a greater number of years thinner and more elastic This is quite the antithesis of the narrow lumen with thick contracted muscle of Western man, all of which cause mechanical stress to the colon wall and the loss of its tensile strength. Bulk additives such as fibre oppose these changes and do so by the absorption of water on to non-digestible residues and by increasing the bacterial mass of the stool and its water content[30,31]. The propulsive effects of motility are easier with moister faeces but this depends on which fibre source is used[32]. Even inert particles[33,34] stimulate colonic function suggesting that the maintenance of an adequate lumen and the size of the faecal bolus are important in normal colonic physiology, the maintenance of which must finally minimize the wear and tear effects on the colon wall which lead to diverticular disease.

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Current hypotheses on synergistic microbial gangrene

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We have reviewed spreading infections of the dermis, with special reference to the importance of synergy in their causation. Evidence for this is accumulating from both clinical studies and from studies in laboratory animals. Necrotizing fasciitis (rapid spread over 24 h) can be caused by β-haemolytic streptococci, sometimes with Staphylococcus aureus, *or by mixed infections of aerobes and anaerobes, often of gut origin. Animal studies provide good evidence that* S. aureus *can potentiate the β-haemolytic streptococcal infection in necrotizing fasciitis. There is also evidence that mixtures of aerobes and anaerobes can act synergistically, but animal models for necrotizing fasciitis have not been developed. Anaerobic cellulitis (variable rate of spread from hours to days) can be caused by mixed aerobes and anaerobes or by mixed clostridia. Animal studies provide good evidence for synergy in the former. Meleney's synergistic postoperative gangrene (slow spread over weeks) may be cutaneous amoebiasis: the animal model of Brewer and Meleney relates to the more rapid infections of anaerobic cellulitis.*

Keywords: Bacterial synergy, anaerobic cellulitis, cutaneous amoebiasis, Meleney's synergistic gangrene, necrotizing fasciitis, streptococcal gangrene

This paper discusses the microbiology of spreading infections of the dermis. This compartment consists of a loose network of fibres containing blood vessels, lymphatics and fat, bounded on one side by the epidermal basement membrane and on the other by the tight connective tissue fascia of the muscle. We wish to draw attention to the evidence that many of these infections seem to be caused by synergy between two or more organisms By synergy we mean that the mixtures of organisms cause more severe infections than each of the organisms singly. By the term mixed infection we imply that the pathogenic effect is no greater than the sum of the damage caused by infection with each organism alone. Clinical isolates often consist of mixtures of organisms and it is common practice to report only the organism that is regarded as the (single) pathogen. We are therefore accustomed to think only of single pathogens. Although there is much evidence that synergy can be important, it is in practice often disregarded.

What evidence is required to establish the role of synergy in these infections? Firstly competent bacteriology needs to be carried out and all the organisms recorded. Many synergistic infections involve anaerobic bacteria and satisfactory techniques for culturing fastidious anaerobes are of fairly recent introduction and are still far from universal. Our experience has been that homogenization of tissue specimens is also important for culture. Valuable additional evidence can be found from serology[1,2], and electron microscopy can show that the tissue contains a mixture of microcolonies of different organisms[3]. Even if it is established, however, that a genuine mixed culture is generally present in these infections, it can always be argued that there is still only a single pathogen and that the other organisms are irrelevant colonizers of necrotic tissue. Thus it becomes essential to establish a convincing animal model to demonstrate synergy. Satisfactory animal models are not easy to establish and need careful analysis. It is very unfortunate that, in our view, the famous animal model of Brewer and Meleney[4] (anaerobic streptococcus and *Staphylococcus aureus*) is unrelated to the disease (Meleney's postoperative 'synergistic' gangrene) which it was developed to explain. Because the crucial difference between the animal model and the disease is the speed of progression of the lesion, we intend to discuss the different clinical syndromes divided into three different rates of progression. Rapidly progressive infections, the first category (e.g necrotizing fasciitis[5–8]), have a time course measured in hours, the second, moderately rapidly progressive infections (e.g. anaerobic cellulitis[5,6]), are measured in days and the third, very slowly progressive infections (e.g. Meleney's postoperative synergistic gangrene[4,9]), are measured in weeks. A simplified summary is given in *Table 1*. It is probable that this grouping of spreading infections of the dermis is an arbitrary division of a continuum The question also arises as to whether very similar syndromes should be differentiated because they are caused by different organisms (c.f. pneumonia).

Rapidly progressive infection (hours)

Human studies

Swartz[6] lists eight syndromes falling under this head of rapidly progressive infections, of which for the present we exclude two as being primarily diseases of the muscle (streptococcal myositis and gas gangrene – clostridial myonecrosis). The remaining syndromes are streptococcal gangrene, necrotizing fasciitis, synergistic cellulitis, non-clostridial anaerobic cellulitis, bacteraemic *Pseudomonas* gangrenous cellulitis and necrotizing cutaneous mucormycosis. These infections are still very serious; Ahrenholz[8] provides a table showing that the mortality rate for necrotizing fasciitis remains unchanged at about 40 per cent Further, these rapidly progressive infections usually need early surgical intervention. We intend to discuss the first two in this section, and the remaining four under the head of moderately rapid progression.

Necrotizing fasciitis begins with a patchy erythema of the skin that is swollen and painful. The edge is not raised and demarcated, as in erysipelas, and lymphangitis is absent. The patient is febrile, later becoming toxaemic, with confusion and disorientation After 24 h, dusky purple areas develop with blistering and bullae, while the erythema and tissue oedema spread further. Rapid necrosis of subcutaneous tissue occurs with deep undermining of ulcerated areas but superficial to the fascial layer. Examination of necrotic tissue shows focal abscess formation with widespread thrombosis of small arterioles and

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Table 1 *Spreading synergistic infections of the dermis and hypodermis*

Clinical entity	Rate of spread	Principal microbial cause	Animal model	Clinical sub-types
Necrotizing fasciitis	Hours	BHS ± *S aureus*	24	Streptococcal gangrene[7,10]
		Mixed aerobes/anaerobes	–	Non-streptococcal necrotizing fasciitis[15–20]
		Mixed aerobes/anaerobes	–	Fournier's gangrene (male genitalia)[13]
		Mouth anaerobes	68, 69	Noma, cancrum oris[14] (mouth)
Anaerobic cellulitis	Hours or days	Mixed clostridia	–	Clostridial anaerobic cellulitis[26,27]
		Mixed aerobes/anaerobes	4, 54 (59–67)	Non-clostridial anaerobic cellulitis[14,28]
Spreading ulcers	Days or weeks			
decubitus		Mixed aerobes/anaerobes[36–38]	–	–
tropical		BHS ± *S aureus*[39,42]	–	–
		Mixed aerobes/anaerobes[40,41]	–	–
diabetic foot		Mixed aerobes/anaerobes[43 44 46]	–	–
Meleney's 'synergistic' gangrene (ulcer)[4,9,53]	Weeks	?*Entamoeba histolytica*[9]	–*	–
Cutaneous amoebiasis[74,75]	(Weeks)†	*Entamoeba histolytica*	(73)	–

Numbers refer to selected references, those in brackets refer to less closely related work. (73) is a review of *Entamoeba*/bacterial interactions, not a description of an animal model, BHS, β-haemolytic streptococci; * we do not consider that Meleney's animal model adequately reproduces the disease, † rapid progression sometimes occurs (reference 74)

venules[7]; adjoining muscle and skin shows comparatively little inflammation. Streptococcal gangrene is the form caused by β-haemolytic streptococcus. The substantial early description by Meleney[10] was of a β-haemolytic streptococcal infection, but in nine of his 20 cases a *Staphylococcus* was also isolated. We cultured *S. aureus* and β-haemolytic streptococcus as a mixed infection from six of 36 patients[7], and Hammar and Wagner[11] from four of eight patients. Other causative organisms in most instances are mixed cultures of intestinal origin[5,6,8], and it is therefore not surprising that this form of necrotizing fasciitis is most commonly (though far from exclusively) associated with abdominal wounds or surgery[5] (including dental drainage[12]). We do not consider this sufficient grounds for making it into a separate clinical entity. The same comment applies to Fournier's gangrene[13] (streptococcal gangrene or necrotizing fasciitis of the male genitalia) and noma (gangrenous stomatitis). Noma is predominantly (but not exclusively) caused by anaerobic bacteria found in the mouth, namely fusiform bacteria and spirochaetes[14]. It is difficult to find good clinical descriptions of the development of this disease, but it probably develops in the submucosal connective tissue of the mouth. However the similarity of this to the dermis and the similarity of the microbiology leads us to classify it with necrotizing fasciitis Further studies on the bacteriology of non-streptococcal necrotizing fasciitis can be found[13,15–23]; others are cited by Feingold[5,14], Swartz[6], Ahrenholz[8] and ourselves[24] Development of reliable anaerobic techniques has shown that the isolation of mixed flora is common in many infections[14]. Direct examination by electron microscopy of necrotic tissue from three patients with necrotizing fasciitis showed that small microcolonies of many different bacteria were scattered throughout the tissue[3]. Thus a genuine mixed infection was present in the tissue and it was not an artefact of sampling. Recent studies with oral bacteria have suggested that co-aggregation may be important in bringing this about[25]

Animal studies

In our animal model for streptococcal gangrene[24] we found that intradermal injection of β-haemolytic streptococcus into the flank of New Zealand white rabbits gave rise to a spreading lesion (cellulitis or necrotizing fasciitis) on only 12 per cent of occasions, but on 50 per cent of occasions when co-injected with an abscess producing strain of *S. aureus* and on 75 per cent of occasions when co-injected with crude staphylococcal α-lysin at a titre which would give inflammation without necrosis Whether or not a given infection produced necrotizing fasciitis or spreading cellulitis depended to some extent on the site of injection. Thus in one group, at the injection site nearest the head, ten spreading lesions developed from 13 injections of which six were diagnosed as necrotizing fasciitis. At other sites there were 13 spreading lesions from 18 injections of which one was so diagnosed. We concluded that synergy with *S aureus* facilitates the development of this rapidly spreading lesion. We did not investigate whether other bacteria or their toxins could substitute for *S. aureus*, or if increased amounts of streptococcal lysins would substitute for staphylococcal α-lysin. There is much animal work suggesting that synergy between aerobic and anaerobic bacteria can have great pathogenic significance, but this fails short of a model for necrotizing fasciitis and will be discussed in the next section.

Progressive infection of moderate rapidity (days)

Human studies

In this section we discuss infections with a variable rate of progression from the moderately rapid to the very rapid. We also include a discussion of spreading ulcers (decubitus, tropical and diabetic foot) becaue of the similarity of their bacteriology

Cellulitis also begins with erythema of the skin that is swollen and painful. Deep blistering and ulceration with necrosis does not occur; superficial blistering, however, can be present The patient may be febrile but is not toxaemic The spreading erythematous edge is diffusely demarcated, but is not raised, while lymphangitis can be present together with lymphadenopathy. In severe cellulitis due to β-haemolytic streptococcus group A or *S. aureus*, patients respond to benzylpenicillin or cloxacillin therapy within 7 days Failure to respond together with incipient necrosis suggests that thrombosis of subcutaneous vessels has occurred.

Clostridial[26,27] and non-clostridial[14] anaerobic cellulitis differ from necrotizing fasciitis in that there is much less pain and systemic toxicity and minimal discoloration of the skin. The two types of cellulitis present very similarly[28]. Clinically it is important to distinguish the condition from incipient gas gangrene and surgical exploration may be required to exclude muscle involvement, followed by debridement[5] The causative organisms of clostridial anaerobic cellulitis are a mixture of clostridia with *Clostridium sporogenes* being that most commonly isolated[26]. Non-clostridial anaerobic cellulitis is usually associated with a mixed flora consisting of two or more of the following: *Escherichia coli, Klebsiella* species, streptococci, anaerobic streptococci and *Bacteroides* species[14,26,28].

Synergistic necrotizing cellulitis[29] can be non-crepitant (due to β-haemolytic streptococcus and *S aureus*), or crepitant, when a variety of gut organisms are isolated, often anaerobic. It is associated with diabetes and there is frequently muscle involvement, thus putting it outside our remit. Swartz[6] regards the crepitant type as a variant of (non-streptococcal) necrotizing fasciitis but it seems to us to be a more severe manifestation of non-clostridial anaerobic cellulitis in which the infection has spread to the muscle. Another syndrome listed by Swartz[6] in this category is infected vascular gangrene which we exclude as being an infection of ischaemic muscle. However, we note that it is commonly a mixed infection (*Proteus* species, *Bacteroides* species, anaerobic streptococci), as is anaerobic streptococcal myonecrosis (anaerobic streptococci and β-haemolytic streptococcus or *S. aureus*[14,26]).

Bacteraemic *Pseudomonas* gangrenous cellulitis and necrotizing cutaneous mucormycosis may be synergistic infections. The latter, also called phycomycotic gangrenous cellulitis, is a rare, rapidly progressive and serious disease[5,30,31]. Correct diagnosis (involving histological demonstration of hyphae) is essential; treatment includes debridement and amphotericin B. Apart from patients with severe burns there is a substantial association with diabetes, or with other diseases with impaired host response[30–32]. In the two cases reported by Wilson *et al.*[32] a variety of bacteria was also present in the infected tissue, but we cannot be certain of the significance of this observation. It is, however, clearly possible that the bacteria may contribute to the pathogenesis. The *Pseudomonas* infections occur in various forms[6,33,34] of which gangrenous cellulitis seems the most relevant. There has also been an account of 48 cases of noma neonatorum associated with *Pseudomonas* septicaemia[35] We are perturbed by the absence of anaerobic bacteriology carried out in studying these severe spreading infections ascribed to *Pseudomonas* species and consider that there is some possibility that they may be the mixed infections of necrotizing fasciitis or non-clostridial anaerobic cellulitis, or that these diseases are subsequently infected by pseudomonads. This is particularly true of noma, which is usually associated with the anaerobic mouth flora[14].

A serious and common ulcer whose possible bacterial causation is rarely discussed is the decubitus ulcer. While the initial step is most probably ischaemic necrosis due to pressure, the bacterial flora is very similar to that of non-streptococcal necrotizing fasciitis or non-clostridial anaerobic cellulitis[36–38]. Its relation to these two syndromes and the animal studies cited later lead us to the opinion that the mixed aerobic and anaerobic bacteria present contribute to the spread of this lesion and are not just irrelevant colonizers of necrotic tissue. Tropical ulcers are interesting in that two types of bacterial flora are reported corresponding to streptococcal and non-streptococcal necrotizing fasciitis, namely β-haemolytic streptococcus and *S. aureus*[39], or mixtures of aerobic and anaerobic organisms (though the anaerobes seem to be predominantly of mouth origin)[14,40,41]. In an earlier paper[42] we suggested that a tropical phagedaenic ulcer might represent localized necrotizing fasciitis caused by β-haemolytic streptococcus. A similar situation occurs in diabetic foot infections though the isolation of β-haemolytic streptococcus seems to be relatively uncommon[43–46].

There are, of course, several spreading bacterial infections of the dermis where only one organism is involved: we are not saying that bacterial synergy is always responsible for spreading infections of the dermis, merely that it often may be Such infections include erysipelas, lupus vulgaris, cutaneous amoebiasis and cutaneous Leishmaniasis. A case of necrotizing fasciitis was reported caused by *Haemophilus influenzae* type b (Reference 22) and various cases of cellulitis have been attributed to it[47,48]. Similar attributions have been made to *Vibrio vulnificus*[21] and to *Aeromonas* species[49,50], both associated with injuries contaminated by polluted water. Erysipelas[2,11] is of interest here in that it is *not* streptococcal necrotizing fasciitis. It is possible that the haemolytic streptococci involved are deficient in some virulence factor or factors, or that these are neutralized by the immune response of the patient. The *Mycobacterium ulcerans* infection (Buruli ulcer) is of interest in that it is a spreading necrotic lesion[51,52]; we feel that synergy with other bacteria should be excluded

Animal studies

Brewer and Meleney[4,53] described an animal model, further investigated by Mergenhagen *et al.*[54], in which cultures of an anaerobic streptococcus and *S. aureus* were injected into the skin of various animals. This resulted in a synergistic infection causing an area of acute gangrene within 48 h. Within 5 days the tissue had separated at the margin and sloughed off. Both organisms were recovered from the lesion. (The original description was of a non-haemolytic microaerophilic *Streptococcus*, but it would only grow properly under anaerobic conditions and its cultural characteristics would now classify it as an anaerobic *Streptococcus*.) This is an important animal model for infections of moderate rapidity. Other experimental studies of mixed infections are of ovine foot rot and the more serious disease infective bulbar necrosis[55–57]. The studies of the latter[55] suggest that a leukocidin produced by *Fusiformis* (*Fusobacterium*) *necrophorus* and a growth factor produced by *Corynebacterium pyogenes* were the agents in the synergy. Studies of necrobacillosis in mice showed that a wide variety of organisms could act synergistically with *F necrophorum*[58]. A study of synergy between *Bacteroides asaccharolyticus* and *Klebsiella pneumoniae* suggested that the agent was a succinate elaborated by the *Klebsiella*[59]. An earlier study[60,61] had shown that a combination of *E. coli* and *Bacteroides fragilis* or *Fusobacterium varium* would give rise to intra-abdominal abscesses in rats when the organisms individually would not. It was also shown that caecal contents would give rise to wound abscesses containing mixed cultures, and pure culture of *B. fragilis* and *B. melaninogenicus* would not, but that the pure cultures mixed with sterile caecal contents also caused abscess formation[61]. Another study showed that *E. coli* and *B. fragilis* could cause wound infections when inoculated at levels at which individually they could not do so[62]. Studies of pelvic inflammatory disease implicate a wide variety of bacteria[63]. Animal studies suggest a synergistic role for mixtures of *Neisseria gonorrhoeae* and *Bacteroides* species, possibly by the promotion of encapsulation of both organisms[64]. There was a general tendency for mixtures of anaerobic and aerobic bacteria to act synergistically[64–67], including *Streptococcus milleri* (*Str. intermedius*) combined with *Bacteroides* species. Other workers[68,69] studied the combination of fusobacteria and spirochaetes found in ulcerative and necrotizing infections of the oropharynx. They found that the two organisms grown together gave many more severe lesions on intracutaneous injection into rabbits than either injected separately. To summarize, there is a considerable body of evidence from animal studies that synergy can be of great importance in these infections, though only some of it[4,24,53,59] refers specifically to spreading infections.

Very slow progressive infection (weeks)

Human studies

In this category we only wish to discuss one syndrome, namely 'Meleney's synergistic gangrene'. Meleney[4,53] described both a disease and an animal model, but we do not consider the two to be related. The human disease described by Meleney is of a severe but very slowly progressing infection, 'extending only one or two centimetres in the course of a week or ten days'. According to Feingold[5]: 'Postoperative progressive gangrene might be a better term, since the infection almost always begins at an abdominal or thoracic operative wound site and frequently where wire retention sutures are employed. The appearance (and bacteriology) are characteristic A few days to a few weeks after operation a tender, red, swollen, and indurated area develops near the wound. This slowly evolves into a shaggy ulcer with gangrenous purple margins fading into an oedematous, erythematous periphery Without treatment the course is one of relentless spread to enormous size with severe pain but little accompanying toxicity. Multiple fistulous tracts and extensive undermining may occur, this lesion, also described by Meleney, has been called chronic burrowing ulcer or Meleney's ulcer.'

However, according to Davson *et al.*[9]· 'Postoperative cutaneous amoebiasis can exhibit precisely similar features. The topography is essentially truncal and the onset often delayed; severe pain and inexorable progression are characteristic. The triple zonation of colour and the serpiginous outline exactly mimic those present in Meleney's synergistic gangrene.

It must be accepted that, clinically, the two entities are indistinguishable and it follows that a certain diagnosis of Meleney's synergistic gangrene is not feasible on clinical grounds'.

Reference to case reports is confusing as this very slowly progressing infection was sometimes confused with the rapidly progressive necrotizing fasciitis or anaerobic cellulitis, and adequate bacteriology was not always carried out. Meleney[70] states that amoebae were not found on histological examination of material from all five of his cases 'by three different well trained parasitologists', but Davson *et al.*[9] draw attention to the need for suitable staining techniques (periodic acid Schiff). Both of these authors draw attention to studies other than Meleney's where amoebae were found. Meleney isolated a 'microaerophilic' *Streptococcus* and *S. aureus* from two of his patients. However, while Davies, Wallace and Irving[71] found the lesion in their patient to be bacteriologically sterile other investigators found various bacteria to be present (e.g. Willard[72] found β-haemolytic streptococcus with *S. aureus* and *E coli*). Thus we cannot accept Feingold's assertion that there is a characteristic bacteriology[5] These possibilities need to be borne in mind in treatment. *Entamoeba histolytica* requires low oxygen levels for growth, and claims have been made of successful treatment with hypebaric oxygen.

We are impressed by the arguments of Davson *et al.*[9] that cutaneous amoebiasis is probably the correct diagnosis of Meleney's synergistic gangrene. There are however some reservations. Cutaneous amoebiasis is rare, even following amoebic abscesses. If *E. histolytica* is the cause of Meleney's postoperative gangrene, then the gangrene should be more common in countries where amoebic infection (or carriage of invasive strains) is more common. We also believe that bacterial cocktails can produce serious disease and could contribute to the pathogenesis of cutaneous amoebiasis; there is also the effect of bacteria on the growth rate and possible pathogenicity of *E. histolytica*[73] It is much to be hoped that all cases diagnosed as Meleney's synergistic gangrene will be studied for both bacterial and amoebic infection using the appropriate methods (cultural, serological and histological). Further information on amoebic disease can be found[73–76].

Animal studies

The animal model[4], which has already been discussed, would seem to relate to non-clostridial anaerobic cellulitis in that it runs a moderately rapid course (gangrene in 48 h, sloughing within 5 days). We do not consider that its rapid progression is relevant to the slowly spreading infection of the human disease Mirelman[73] cites evidence that bacteria can affect the virulence of *E. histolytica.*

Conclusions

Present incomplete knowledge suggests that many spreading infections of the dermis are caused by a mixture of bacteria acting synergistically. The area has been a difficult one. The relatively infrequent occurrence of cases has the result that consensus as to what is a significant syndrome is only slowly reached. Further the grouping into syndromes is probably an arbitrary division of a continuum and each syndrome may have a variety of microbial causes. The bacteriological aspect has been handicapped by two facts. One is the fairly recent introduction of satisfactory techniques for handling the fastidious strict anaerobes which are still not available in all microbiology laboratories The other is the strong inbuilt assumption that microbial diseases have a single microbial cause, and that other organisms isolated are irrelevant. This last assumption is an aspect of the important principle of Occam's razor[77] (*'entia non sunt multiplicanda praeter necessitatem'* – no more things should be presumed to exist than are necessary), but we think we have demonstrated that it is necessary to consider bacterial synergy. Thus we hope there will be further studies on a substantial number of well characterized patients using good anaerobic techniques and with necessary back up from serology, histology and electron microscopy. All isolates should be considered potentially synergistic, but this can only be demonstrated in animal models which properly reproduce the infection within an appropriate time period. We summarize our views in *Table 1* but recognize that it will need revision. However we hope it provides a continuing basis for debate.

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Pouch size: the important functional determinant after restorative proctocolectomy

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Sixty-seven patients with a J-shaped ileoanal pouch were studied over a 2-year period with regular recording of sphincter and pouch characteristics and analysis of their role in functional outcome. Although there was a 27 per cent permanent reduction in resting anal pressure (RAP) ($P<0{\cdot}001$)*, two-thirds of the patients still had a RAP within the normal range. The mean(s.d.) pouch volume increased during the first year from 132(46) ml to 282(85) ml. RAP was not related to functional outcome and preoperative RAP was not predictive of subsequent function. Large pouch volume and compliance correlated with low defaecation frequency (range of* $r=0{\cdot}27$–$0{\cdot}36$; $P<0{\cdot}05$) *and good overall function* ($r=0{\cdot}37$–$0{\cdot}56$; $P<0{\cdot}01$)*. The initial pouch volume was predictive of subsequent overall function. The ileal length used for pouch construction predicted subsequent pouch volume* ($r=0{\cdot}48$; $P<0{\cdot}001$) *and to some extent functional outcome* ($r=0{\cdot}28$–$0{\cdot}37$; $P<0{\cdot}05$)*. However, the studied variables accounted for only 21 per cent of the total variance of functional outcome.*

Keywords: Restorative colitis, restorative proctocolectomy, anal pressure, pouch capacity

Restorative proctocolectomy, i.e. colectomy, mucosal proctectomy and ileal pouch-to-anus anastomosis, has become the principal method of surgical treatment for ulcerative colitis in many specialized centres. With modifications in technique and increased experience, the complication rate has decreased and functional results have improved. Functional imperfections are still frequent however, such as excess stool frequency, the need for nocturnal evacuation and episodic soiling of underwear[1]. Possible causes of such impairment are sphincter damage from endocavitary mucosal dissection[2–4], sacrifice of the transitional zone in the anal canal[5–8], insufficient pouch capacity[9–11] and improper pouch dynamic characteristics[12–15], with disturbance of rectoanal reflex control. To what extent they each or in combination contribute to the clinical result remains controversial A long-term clinicophysiological evaluation has therefore been conducted in a consecutive series of patients operated on by restorative proctocolectomy with construction of a J-configurated pouch. The principal aim was to study, by means of a specially designed manovolumetric technique, the changes in sphincter status and pouch characteristics with time, during the first 2 years after surgery, in an attempt to analyse which factor(s) might determine the clinical result

Patients and methods

Sixty-nine patients underwent restorative proctocolectomy (ileoanal anastomosis with J pouch) between August 1982 and July 1986. Two patients were excluded because of failure The remaining 67 patients, 63 with ulcerative colitis and four with polyposis, comprised 35 men and 32 women of mean age 35 years (range 17–59 years) Thirty patients had the ileoanal anastomosis performed as a primary procedure, whereas the remainder had previously undergone colectomy with ileorectal anastomosis (11 patients), intra-abdominal closure of the rectum (eight patients) or construction of a proctostomy (18 patients) The mean(s d) length of the ileal segment used for pouch construction as measured at operation was 16(3) cm (range 12–30 cm). All pouches were handsewn. Mucosectomy was performed from below using a Park's retractor[1] and starting at the dentate line The rectal muscular cuff was divided 1–2 cm above the puborectal sling. The ileoanal anastomosis was performed using interrupted polyglycolic acid (Dexon®, Davis and Geck, Gosport, UK) sutures. A protecting loop ileostomy was closed at a mean of 12 weeks (range 6–52 weeks) after the operation No changes were made in the operative technique during the study.

Anorectal manovolumetry was performed before operation, immediately before closure of the loop ileostomy, and at 1, 3, 6, 12 and 24 months after ileostomy closure. On each occasion full particulars about the clinical condition were also noted. Recording of the number of bowel movements and occurrence of soiling was based on diaries of self-monitoring kept for 2 weeks before each visit. Functional variables were graded according to an arbitrary score designed to quantify the overall functional result (*Table 1*) Because of late failure with conversion to ileostomy (three patients), removal abroad, or lack of interest in further participation, 67 patients were investigated at the 1 month follow-up and

Table 1 *Scoring system designed to quantify overall function*

	Score*		
	0	1	2
No. of bowel movements			
Daytime	≤4	5	≥6
At night	0	>1/week	≥2/night
Urgency (inability to defer evacuation >30 min)	No	Yes	
Evacuation difficulties (>15 min spent in toilet on any occasion during the week)	No	Yes	
Soiling or seepage			
Daytime	No	>1/week	
At night	No	>1/week	
Inability to release flatus safely	No	Yes	
Perianal soreness	No	Occasional	Permanent
Protective pad			
Daytime	No	>1/week	
At night	No	>1/week	
Dietary restrictions (avoid certain items that interfere with pouch function)	No	Yes	
Medication (continuous or occasional)	No	Yes	
Social handicap (not able to resume full-time occupation or participate in social life)	No	Yes	

* Score range 0–16: overall good function scores 0 points, overall poor function scores 16 points

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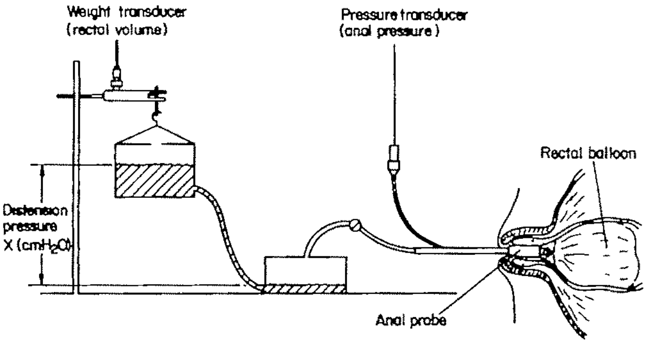
Weight transducer (rectal volume)
Pressure transducer (anal pressure)
Rectal balloon
Distension pressure X (cmH_2O)
Anal probe

Figure 1 *Schematic illustration of the manovolumetry set up The volume change of the balloon was monitored as weight change (1 g = 1 ml) of a water reservoir, suspended on a force displacement transducer (Grass FT 10 C, Grass Medical Instruments, Massachusetts, USA) and used to effect distension of the balloon via an air reservoir. Anal pressure was recorded using a disposable endotracheal tube (Mallinckrodt No. 7, external diameter 10 mm, Mallinckrodt, Laboratories Ltd., Athlone, Ireland) threaded on the tubing between the air reservoir and the rectal/pouch balloon. The cuff of the endotracheal tube which served as an anal probe was filled with water and connected to a Statham pressure transducer (P 23 D, Statham, Gould Inc., California, USA)*

63, 65, 64 and 58 patients at the 3, 6, 12 and 24 month follow-ups respectively.

Anorectal/pouch manovolumetry was performed using a device that permits simultaneous recording of anal pressure and rectal volume during isobaric distension of the rectum by means of a high compliance polyethylene balloon. The balloon was 12 cm long and had a maximal volume of 600 ml when insufflated with air The details[16] are shown in *Figure 1*. Anal pressure and rectal pouch volume were recorded on a Grass® polygraph (Grass Medical Instruments, Massachusetts, USA). No bowel preparation was used but patients were asked to empty the rectum/pouch and bladder before each investigation The investigation was performed in the left lateral position. The distension pressures used were 20, 40, 60 and 80 cmH_2O The balloon was emptied between each distension, which was maintained for 60 s Maximal pouch volume was defined as maximal volume recorded during distension at 80 cmH_2O, which was commonly associated with low abdominal or pelvic discomfort or urge to evacuate. Compliance was calculated as volume increase (ml)/pressure increase (cmH_2O) in the four intervals between zero and 80 cmH_2O.

Anal resting and squeeze pressures obtained from 36 healthy controls matched for age and sex (mean(s d) age 31(5) years, range 23–42 years; 17 men and 19 women) were used for comparison

The study was approved by the Ethical Committee of the University of Goteborg

If not otherwise stated, results are presented henceforth as mean(s.d.) with one degree of freedom. Statistical analysis included Student's *t* test comparing means Correlations were sought using linear simple and stepwise regression analysis ($P<0{\cdot}05$ was considered significant).

Results

Manovolumetric investigations

Resting anal pressure. The changes in resting anal pressure (RAP) appear in *Figure 2* When measured before ileostomy closure, RAP was 45(13) mmHg (range 12–75 mmHg), compared with 71(16) mmHg (range 37–117 mmHg) before restorative proctocolectomy ($P<0{\cdot}001$). Although a slight increase was observed with time, a RAP at 1 year of 52(15) mmHg (range 23–90 mmHg) was still significantly below the preoperative level ($P<0{\cdot}001$), corresponding to a 27 per cent decrease. No further improvement was demonstrated after 1 year. Postoperative changes in RAP appeared to be unrelated to type of previous operation (one or two staged), patient age or sex.

RAP before restorative proctocolectomy (71 mmHg) was higher than in healthy controls (61(8) mmHg; 95 per cent prediction limits 46–77 mmHg; $P<0{\cdot}001$), while postoperative RAP at 1 year (52 mmHg) was significantly lower than in controls ($P<0{\cdot}001$). Four patients had a preoperative RAP below the 95 per cent prediction limit for controls, while RAP was below that level in 21 patients at the 1 year follow-up.

Of 64 patients, 52 (81 per cent) were still on loperamide medication at the 1 year follow-up. RAP in these patients (54(14) mmHg) was higher than in those not taking retarding drugs (43(17) mmHg) ($P<0{\cdot}05$).

Maximal squeeze pressure. Preoperative maximal squeeze pressure (MSP) was 150(26) mmHg in female patients and 262(62) mmHg in male patients ($P<0{\cdot}001$). MSP decreased after operation to 131(28) mmHg ($P<0{\cdot}01$) and 243(53) mmHg (not significant) respectively, but subsequently recovered to preoperative levels (*Figure 2*). Pressure levels both before and after surgery compared well with those of healthy controls.

Pouch volume and compliance. Before ileostomy closure maximal pouch volume (at 80 cmH_2O) was 132(46) ml (range 50–315 ml), and at 1 year it was 282(85) ml (range 70–445 ml). No further volume increase was observed after 1 year. The most marked expansion occurred during the first 6 months after ileostomy closure (*Figure 3*). Pouch distension with 20 cmH_2O caused a volume increase of about 50 per cent of the maximal volume Pouch compliance also increased with passage of time. At 1 year it was 8·6 ml/cmH_2O in the pressure interval 0–20 cmH_2O, 3·0 ml between 20 and 40 cmH_2O, 1·3 ml between 40 and 60 cmH_2O and 1·1 ml between 60 and 80 cmH_2O distending pressure.

Although pouch volume varied over a wide range at all intervals (*Figure 4*), there was a significant correlation between maximal pouch volume recorded before ileostomy closure and that at 1 year ($r=0{\cdot}62$; $P<0{\cdot}001$). That is, a low initial pouch volume was indicative of a subsequent low volume reservoir. The length of ileal segment used for pouch construction correlated with the subsequent maximal pouch volume ($r=0{\cdot}48$, $P<0{\cdot}001$) (*Figure 5*). However, the magnitude of pouch expansion could not always be explained by the length of the ileal segment. Analysis of the influence of preoperative history, the need to sever mesenteric vessels, and postoperative complications failed to reveal any obvious causes for the difference in volume between reservoirs with identical segment length; nor did RAP correlate to pouch volume. In contrast the presence of pouchitis was associated with a lower reservoir volume. Eight patients with a maximal reservoir volume of 215(78) ml had pouchitis around the 1 year follow-up, compared with 54 analogous patients without pouchitis who had a reservoir volume of 292(82) ml ($P<0{\cdot}05$). Eighteen patients had had episodes of ileitis before (but not around) the 2 year follow-up, and at that time these had a maximal reservoir volume of 259 ml, compared with 305 ml for those who had never suffered from the condition ($P=0{\cdot}09$). It was also observed that patients who were

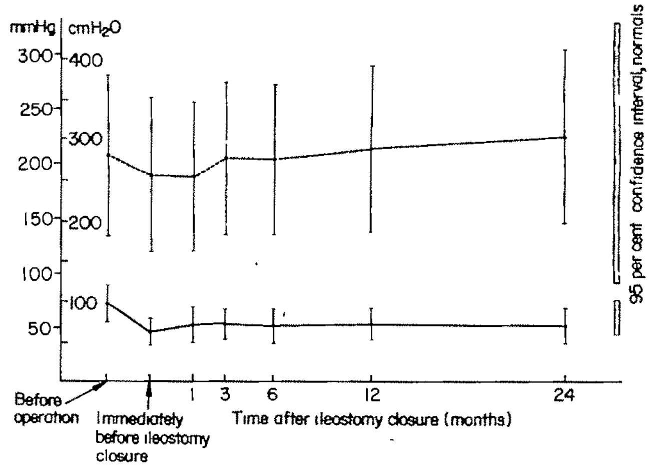

Figure 2 *Resting anal pressure (—) and maximal squeezing capacity (---) at intervals Note the 95 per cent prediction limits for normals*

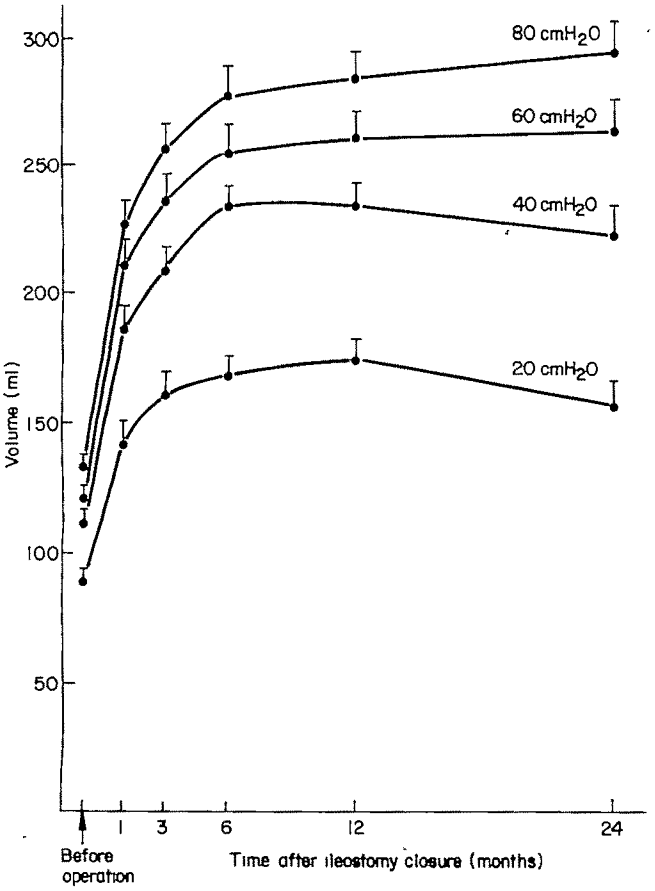

Figure 3 *Pouch volume at distension pressures from 20 to 80 cmH$_2$O at intervals after loop ileostomy closure (mean(s.e.m.))*

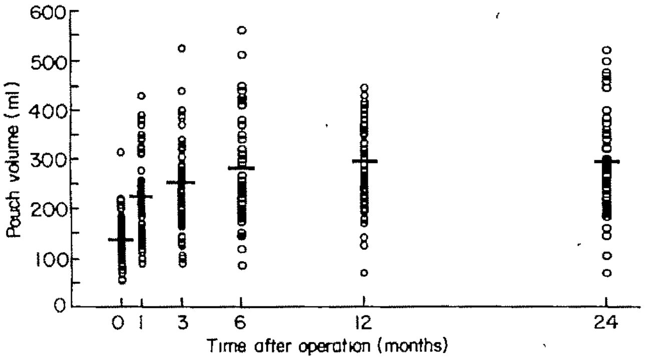

Figure 4 *Individual maximal pouch volumes (at 80 cmH$_2$O distension pressure) at intervals after loop ileostomy closure (bars indicate median values)*

on loperamide had a lower pouch volume than the others (269(77) ml *versus* 342(97) ml, $P < 0{\cdot}01$, at 1 year).

Reflex sphincter inhibition on rectal distension was clearly present in all patients before operation. When studied both at the time of ileostomy closure and 1 month later, pouch distension was not associated with such a sphincter response. However, an unequivocal reduction in sphincter pressure could be demonstrated in three patients 6 months after surgery. At 1 year another three patients exhibited a similar response, and 2 years after operation reduction in sphincter pressure on pouch distension was observed in 15 of the 58 patients investigated.

Functional outcome related to manovolumetric data

Mean defaecation frequency decreased gradually with the passage of time, stabilizing within a year at about five evacuations per 24 h. Beyond that time no further improvement was observed. The frequency of the functional defects on which the functional score calculation was based appears in *Tables 2* and *3*. The overall functional score declined from 8·0 initially to 4·5 at 1 year and to 4·0 at 2 years. If not otherwise stated, the comparative results of the manovolumetric characteristics and the functional outcome are based on the 1 year follow-up as no further changes occurred in the manovolumetric variables beyond this time.

Functional results versus *resting anal pressure and maximal squeeze pressure.* None of the individual functional variables in the score list (*Table 1*), except the use of loperamide, appeared to be related to RAP, even in patients with an anal pressure below the 95 per cent prediction limit for healthy controls (<46 mmHg). Although patients with day and/or night soiling exhibited a lower anal pressure compared with those without such defects, this difference failed to reach statistical significance The overall functional result, as reflected by score, correlated neither with resting nor with maximal sphincter pressure at any

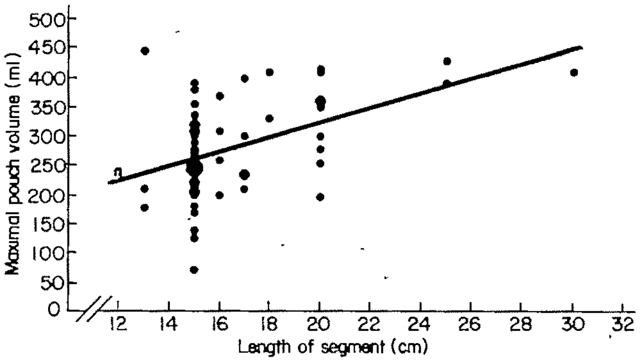

Figure 5 *Length of pouch segment at construction* versus *pouch volume 12 months after loop ileostomy closure,* $r = 0{\cdot}48$, $P < 0{\cdot}001$ ($y = 12{\cdot}3x + 77{\cdot}7$)

Table 2 *Variables at 1 year and 2 year follow-up*

Evacuation frequency	1 year	2 years
Day		
Mean	4·5	4·6
Range	2–11	2–12
Interquartile range	3–5	4–5
Night		
Mean	0·5	0·4
Range	0–3	0–2
Interquartile range	0–1	0–1

Table 3 *Variables scored at 1 year and 2 year follow-up*

	Percentage of patients	
	1 year	2 years
Urgency	8	3
Evacuation problems	5	2
Soiling during the day	23	24
Soiling at night	30	22
Unsafe release of flatus	47	36
Soreness	34	26
Pad during the day	38	36
Pad at night	61	55
Dietary restriction	10	9
Medication	82	79
Social handicap	5	5

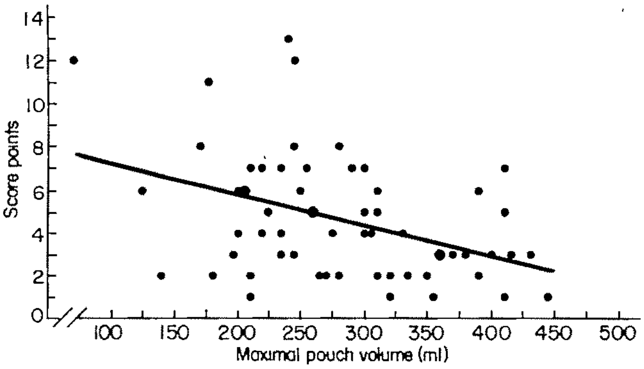

Figure 6 *Maximal pouch volume* versus *score points at 1 year follow-up*, $r=0{\cdot}42$, $P<0{\cdot}001$ ($y=-0{\cdot}14x+8{\cdot}7$)

postoperative interval. Moreover, the preoperative anal pressure was not predictive of subsequent function.

Functional result versus *pouch capacity and anal sphincter response.* A high evacuation frequency correlated with a small pouch volume at all follow-up times (range of r=0·27–0·36; P=0·037–0·004), and daytime soiling, day and night use of protective pads and the need for retarding drugs were also related to a low pouch volume. While the need for night evacuation and night soiling were both more common in patients with smaller pouches than in those with larger pouches, this difference failed to reach statistical significance. A small pouch volume correlated with a high functional score, reflecting a less satisfactory overall function (r=0·37–0·56; P=0·0057–0·0001) (*Figure 6*). A similar correlation was also found between compliance and functional outcome. Although low early pouch volume, i.e. the volume recorded before ileostomy closure, indicated a subsequent poor overall functional result, the initial pouch volume appeared not to be predictive as regards the future defaecation frequency. The length of ileum used for pouch construction showed a weak but significant negative correlation with functional score (r=0·28–0·37, P=0·0327–0·0024)

When comparing functional outcome in patients with and without reflex sphincter pressure reduction on pouch distension, no significant difference could be demonstrated. In a stepwise regression analysis of the variables, and with functional score as the dependent variable, maximal pouch volume and compliance were identified as the only two significant factors. They accounted for 21 per cent of the total variance of the functional score at the 1 year follow-up (adjusted r^2=0·21).

Discussion

Previous clinical and physiological studies, on patients subjected to restorative proctocolectomy with an ileal pouch-to-anus anastomosis, have produced conflicting results about the role of anal sphincter status and pouch characteristics in subsequent functional outcome. It has been suggested that the postoperative decrease in resting anal tone contributes to imperfection in continence[2] and that it is partly or entirely caused by overstretching the sphincters during the procedure[4] Faecal or mucous soiling has been demonstrated more frequently in patients with low anal pressure[2,17–19].

The results of the present study confirm previous observations that, although squeeze pressure recovered eventually, RAP was markedly reduced initially and, despite a gradual improvement with time, at 1 year it remained significantly reduced below the preoperative level by about 25 per cent.

In contrast to most previous studies, however, no significant correlation could be demonstrated between low anal pressure and imperfection of continence. One explanation for the divergent result in this study may be that the reduction in sphincter tone was less pronounced compared with that reported by others Two-thirds of the patients in the present study at 1 year follow-up had a RAP within the 95 per cent prediction limit for matched healthy controls, implying that the internal sphincter function had been reasonably well preserved. This is in concert with those authors who have reported modest reductions in RAP and who have been unable to demonstrate any correlation between anal pressures and continence[15,20] The observation that loperamide medication, which was used by more than 80 per cent of our patients, was associated with a comparatively high RAP might be relevant in this respect. It has been suggested that this agent increases internal sphincter tone[21].

While the internal anal sphincter, which is responsible for about 80 per cent of anal resting tone[22], is important for continence under normal circumstances, this may not be so in the new artificial setting. There is evidence that continence in ileoanal pouch patients in whom the internal sphincter has been partly[23] or even entirely removed[24,25] is still reasonably well preserved. It appears likely therefore that imperfection in continence, often characterized by minor soiling, is not caused by a low resting tone *per se*, but may rather be due to postoperative deformity in the anal canal, a factor well known to interfere with anal continence after surgical treatment of haemorrhoids, fistulae and fissures. Loss of anal cushions[26] and the anal transitional zone with its unique sensory nerve endings[27] as well as the presence of full thickness ileum within the anal canal[7] may also contribute. It has been suggested that preservation of the transitional zone above the dentate line will reduce the risk of incontinence[6].

The present results show that the squeeze contraction was similar in both patients and controls, and agree with the findings of others[3,14,23] suggesting that striated muscle is not affected by the endocavitary proctectomy. Preservation of striated muscle function, including the important puborectalis sling, might contribute to the fact that the majority of patients enjoy good confidence, because it promotes effective closure of the junction between pouch and anal canal, both at rest and during sudden increases of intra-abdominal pressure.

While the relationship between sphincter status and functional result may be less convincing, the present results clearly show that the functional outcome is related to the volume and compliance of the pouch. In this respect the results are in accordance with most previous reports[14,19,28], implying that pouch volume is a determinant not only for evacuation frequency but also for continence. The present results convincingly demonstrate that the larger the pouch volume the better is the functional result, both in terms of individual functional markers and as reflected by the overall functional score.

Unfortunately differences in methodology do not allow for a reliable comparison of data on pouch capacity between different authors. Determination of pouch volume at standardized graded pressure levels, as performed in the present study during isobaric conditions, would have allowed a more accurate assessment of true pouch capacity and compliance than the traditional studies using stepwise volume increments of balloon distension with endpoint maximal tolerable volume. In the present study, regular follow-up revealed a rapid expansion of pouch volume over the first 6 months, with no further change beyond 1 year. At that time the J pouch had doubled its initial volume and the maximal volume approached an average of 300 ml. This is in agreement with the findings of other authors[28] The compliance of the pouch was highest in the lowest pressure interval, amounting to about 8 ml/cmH_2O This finding implies that the J pouch can utilize at least 50 per cent of its maximal volume at a distension pressure that is not appreciated by the patient, and is in agreement with recently published results[29].

Although the capacity of the pouch generally increased with time and with increasing length of intestine used for its construction, this was not always the case. A separate analysis of patient and operative factors failed to reveal any obvious cause for this variance in pouch expansion. It appears reasonable to assume, however, that intrapelvic adhesions or fibrosis and variations in dimensions and viscoelasticity of the intestine may be factors that limit pouch volume expansion. The observation that a low early pouch volume was predictive of a future low-capacity pouch with a subsequently poor overall function result supports this view. Moreover, it has been demonstrated recently that the pelvic space itself may be an important variable that determines pouch expansion[30]. The results of the present study imply that pouchitis, apart from causing watery, voluminous stools, may influence pouch function adversely by reducing its volume capacity.

Apart from alternative techniques for the perineal phase of the operation several different pouch designs have been on trial in an attempt to improve results[4,7,9,30,31]. There is clinical evidence that the S-shaped reservoir attains a larger capacity than the J-shaped reservoir and that this is associated with better function. The W-configurated pouch is reported to be superior both to the J and S pouches[12,32]. Whether these differences in volume and function are attributed to the dynamics of the pouch or simply to different lengths of ileum used is controversial[11]. The observation that increasing length of the ileal segment used for construction of the pouch correlated with a favourable functional outcome supports the latter view One should be aware, however, that pouch characteristics could in this study account for only a fraction of the total variance of functional outcome ($r^2=0{\cdot}21$). Similar results have been presented by Becker and Raymond[28]. We have previously demonstrated that age is a determinant for functional outcome[1]. Adding age to the present stepwise regression model of manovolumetric variables against functional score gave $r^2=0{\cdot}30$.

Although pouch volume and bowel frequency change very little after 6 months, the results of the present study imply that the overall functional result reflected in the score calculation improved further beyond that time. This improvement might be explained by a general and gradual functional adaptation, but the changes in the patients' social habits must also be taken into account. It appears very likely that patients will learn by trial and error to adopt dietary restrictions to make firmer stool and the change the timing of meals to gain control over defaecation habits. For example, many patients find that they can avoid night evacuations by bringing forward the timing of the final evening meal. Such measures, as well as the use of motility-retarding drugs and bulk agents, may have an important impact even on continence.

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Double contrast barium enema and flexible rectosigmoidoscopy: a reliable diagnostic combination for detection of colorectal neoplasm

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The efficiency of double contrast barium enema and flexible rectosigmoidoscopy (to 60 cm) in the assessment of patients with a positive Hemoccult II® test in a randomized screening study for colorectal neoplasms was evaluated. A positive test was present in 625 patients, of whom 530 had a complete enema and rectosigmoidoscopic assessment. A carcinoma was diagnosed in 26 and an adenoma ⩾1 cm in diameter in 71. As a control, 323 patients with a negative assessment repeated the Hemoccult II test and of these 67 had a positive second test, of whom 55 underwent colonoscopy. One carcinoma (Dukes' A) and two adenomas ⩾1 cm in diameter were diagnosed. The efficiency of the assessment was also checked by rescreening the whole group 1–2 years after the first study and by continuing follow-up. It was found that two more carcinomas and one adenoma ⩾1 cm in diameter had been overlooked at the primary assessment. The sensitivity for neoplasms ⩾1 cm in diameter at the primary assessment was 72 per cent for double contrast barium enema and 86 per cent for rectosigmoidoscopy. The sensitivity for the combined methods was 94 per cent and the specificity was 99 per cent. The combination of double contrast barium enema and rectosigmoidoscopy in the primary assessment of patients with a positive Hemoccult II test gives an acceptable result and immediate retesting of those with a negative assessment is not necessary.

Keywords: Screening, colorectal neoplasm, rectosigmoidoscopy, barium enema

In a screening study for colorectal neoplasms, three factors are of fundamental importance[1]. First, compliance must be high since, if only a small proportion of the population participates, the screening will be worthless. Second, the screening test must have a high sensitivity and an acceptable specificity. Finally, the assessment strategy for detection of cancer in persons with a positive test must be accurate and the methods used must be reasonably acceptable to patients.

Since 1982, a prospective randomized screening study for the detection of colorectal neoplasms using faecal occult blood testing has been under way in Göteborg, Sweden[2]. This study includes 51 325 patients between 60 and 64 years of age. Those with a positive test have been assessed with flexible rectosigmoidoscopy (to 60 cm) and double contrast barium enema.

The purpose of the present study was to evaluate the efficiency of the assessment strategy. This was done by re-examination of patients with a negative primary enema and rectosigmoidoscopic assessment but with a continuing positive Hemoccult II test. The re-examination consisted of colonoscopy and radiography of the stomach. This expanded assessment, together with rescreening and follow-up of the patients, allowed an evaluation of the efficiency of the primary assessment strategy.

Patients and methods

The patients had been enrolled in two continuing randomized screening studies of persons between 60 and 64 years of age for the detection of early colorectal cancer in the city of Göteborg All 27 770 inhabitants born between 1918 and 1922 were randomly allocated to a control or a test group (13 759 persons in the test group) The first screening was performed between August 1982 and December 1983. All patients still alive in the test group were offered rescreening, which was performed between March 1984 and December 1985 The second study was identical to the first and included all inhabitants born between 1 January 1923 and 1 July 1925 These patients were also randomly allocated to a control ($n=6249$) or a test group ($n=6204$) This screening was started in January 1987 and was completed in November 1987. The rescreening was performed between March and December 1988.

Three slides of Hemoccult II® test (Smith Kline Diagnostics, Incorporated, Sunnyvale, California, USA), a letter of instruction and a prepaid reply envelope were mailed to all the patients in the test groups. They were instructed to exclude from their diet fresh fruit and vegetables, vitamin C and food containing blood for two days before testing Two samples were taken from each of three consecutive stools. After the last sample, the slides were immediately mailed back to the hospital for evaluation. All slides except those used in the first screening series (from persons born between 1 January 1918 and 31 June 1920) were rehydrated before development The test was considered positive if one or more of the six samples indicated the presence of blood All patients with a positive Hemoccult II test were offered proctoscopy, rectosigmoidoscopy (to 60 cm) and double contrast barium enema Only neoplasms and inflammatory bowel disease were regarded as possible sources of bleeding All excised neoplasms were examined by the same pathologist and the adenomas were measured before fixation. The examining radiologist reported only a no or yes answer If a lesion had been seen only on the radiographs, either a repeat double contrast barium enema or colonoscopy was performed Patients with a negative assessment were asked to perform a second Hemoccult II test series If this second test was positive, they were further investigated with colonoscopy and also offered radiography of the stomach Those with a negative Hemoccult II result at the repeat test were not further investigated until they were offered rescreening

All individuals in the test and control groups were continuously followed using the local cancer and death registers, weekly reports from the local city hospitals and the register at the Department of Pathology.

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Any symptomatic colorectal neoplasm not found at screening should have been detected in this way.

Results

Hemoccult II tests were mailed to 19963 patients and 13147 (66 per cent) performed the test. *Figure 1* shows that 625 patients had a positive test, of whom 530 (85 per cent) were assessed with double contrast barium enema and rectosigmoidoscopy and 38 (6 per cent) were assessed with rectosigmoidoscopy alone. A total of 372 patients had a negative assessment and were asked to repeat the Hemoccult II test; 323 (87 per cent) did so. The repeat test was negative in 256 patients who were not further investigated. In 67 patients the test was positive and they were offered colonoscopy; 55 of them underwent this examination.

Altogether 29 patients, with 29 carcinomas, were identified at assessment of those with a positive Hemoccult II test. Twenty-six of the carcinomas were diagnosed at the primary assessment and three were initially overlooked (*Table 1*).

In all, 153 adenomas were diagnosed in 120 patients. The adenomas were ≥1 cm in diameter in 74 patients All but three of these adenomas were diagnosed by rectosigmoidoscopy and/or double contrast barium enema at the primary assessment (*Table 1*). An inflammatory bowel disease was diagnosed in nine patients.

Ten out of a total of 26 carcinomas in the rectosigmoid region and one of three carcinomas located above the sigmoid area were missed with double contrast barium enema (*Table 2*). Four of the 26 carcinomas in the rectosigmoid region were overlooked at rectosigmoidoscopy Eighteen (26 per cent) of 69 adenomas with a diameter of ≥1 cm and located in the rectosigmoid area were overlooked at double contrast barium enema. The corresponding figure for rectosigmoidoscopy was nine (13 per cent) (*Table 2*).

Five neoplasms were found at colonoscopy in five patients (one Dukes' A sigmoid carcinoma and four adenomas, two of which were ≥1 cm in diameter and located in the sigmoid colon). The carcinoma was overlooked both at rectosigmoidoscopy and at double contrast barium enema (*Table 1*).

All patients with a positive Hemoccult II result on repeat testing were also offered a radiographic examination of the stomach. Of 55 patients, 43 accepted this examination, which was normal in all cases (*Figure 1*).

All patients were offered rescreening, which was performed 11–22 months after the first investigation, with a compliance of 58 per cent. Ninety-three per cent of those who took part in rescreening had participated in the first screening. One carcinoma and one adenoma ≥1 cm in diameter were found on rescreening (*Table 1*). The patient with the carcinoma had had a sigmoid adenoma removed at the first screening and was therefore not retested The carcinoma was located 10 cm above the polyp and was not reached at the primary sigmoidoscopy due to residual faeces from faulty bowel preparation. This carcinoma was also overlooked at double contrast barium enema.

Follow-up from the time of first testing ranged from 4 to 5·5 years for patients in the first group and from 1 to 2 years for those in the second group During follow-up one caecal carcinoma was found which had been overlooked at double contrast barium enema due to perception error (*Table 1*). The repeat Hemoccult II test was negative in this patient.

The prevalence, sensitivity, specificity and predictive values for the primary assessment programme (rectosigmoidoscopy and double contrast barium enema) for carcinomas and adenomas ≥1 cm in diameter are shown in *Tables 3* and *4*

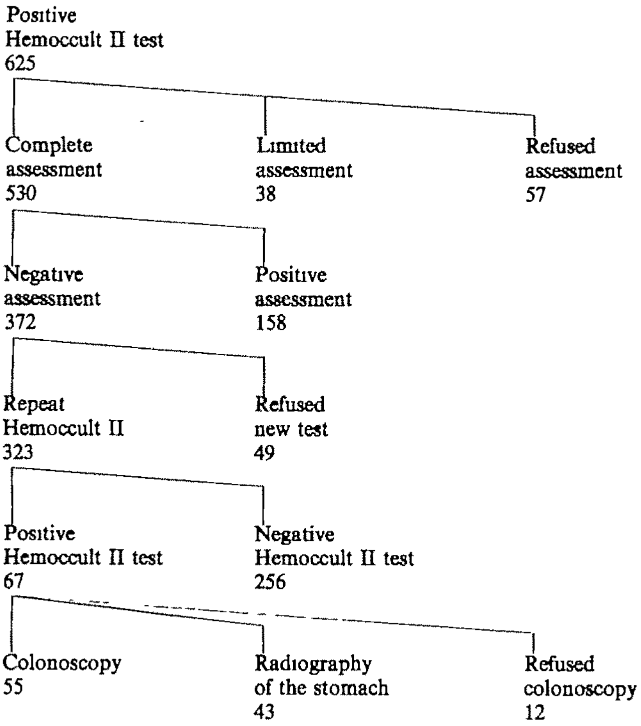

Figure 1 *Distribution of patients in the test group with positive Hemoccult II test*

Table 1 *Number of subjects with carcinomas and adenomas diagnosed at primary assessment, colonoscopy, rescreening and follow-up*

	Carcinoma	Adenoma ≥1 cm
Primary assessment	26	71
Colonoscopy	1	2
Rescreening	1	1
Follow-up	1	0
Total	29	74

Table 3 *Diagnostic accuracy of combined double contrast barium enema and rectosigmoidoscopy assessment for carcinomas of the large bowel*

	Number with colorectal carcinoma	Number without colorectal carcinoma
Positive assessment	26	0
Negative assessment	3	501

Prevalence, 29 of 530 = 5·5%; sensitivity, 26 of 29 = 90%

Table 2 *Diagnostic accuracy of rectosigmoidoscopy and double contrast barium enema for carcinomas and adenomas of at least 1 cm in diameter in the rectosigmoid area*

	n	Overlooked by double contrast barium enema	Overlooked by rectosigmoidoscopy	Overlooked by both methods
Carcinomas	26	10	4	2
Adenomas	69	18	9	3

Table 4 *Diagnostic accuracy of combined double contrast barium enema and rectosigmoidoscopy for adenomas at least 1 cm in diameter in the large bowel*

	Number with colorectal adenoma	Number without colorectal adenoma
Positive assessment	71	4
Negative assessment	3	452

Prevalence, 74 of 530 = 14%, sensitivity, 71 of 74 = 96%, specificity, 452 of 456 = 99%

Discussion

Colonoscopy is regarded by some as the gold standard, with a sensitivity exceeding 90 per cent[3]. Others claim that up to 30 per cent of colonoscopies are so technically difficult that follow-up has to combine rectosigmoidoscopy and double contrast barium enema[3]. Furthermore, the possibility of missing neoplasms of even 1–2 cm in diameter at endoscopy has been clearly demonstrated[4,5], suggesting that colonoscopy alone is an improbable gold standard. Nevertheless, colonoscopy is superior to double contrast barium enema, in that its specificity is close to 100 per cent and it allows adenomas to be removed during the examination.

Colorectal neoplasms are also easily overlooked by double contrast barium enema, even when the examination is of high technical quality. Perception error is the most common cause of misjudgement and the sigmoid and right colon seem to be the most difficult to examine satisfactorily[6–9]

In the present study a meticulous follow-up has been undertaken to diagnose neoplasms possibly overlooked at the primary assessment. As the Swedish health system does not allow a patient to be treated by a doctor outside his own community, virtually all patients can be followed up by the methods used. Two-thirds of the patients have been followed for at least 5 years and one-third for at least 2 years. It is therefore reasonable to assume that the numbers of overlooked carcinomas and larger adenomas were small.

The sensitivity for detection of carcinoma in the whole of the large bowel was only 62 per cent (18 of 29) for double contrast barium enema. For detection of carcinoma in the rectosigmoid area the sensitivity of rectosigmoidoscopy was 85 per cent (22 of 26). The sensitivity increased to 90 per cent (26 of 29) when the two diagnostic methods were combined.

The sensitivity for detection of adenomas with a diameter of $\geqslant 1$ cm in the large bowel was 76 per cent (56 of 74) for double contrast barium enema. For detection of adenomas in the rectosigmoid area the sensitivity of rectosigmoidoscopy was 87 per cent (60 of 69). When the results of double contrast barium enema and endoscopy were combined, the sensitivity increased to 96 per cent

Specificity for carcinoma and adenoma respectively of double contrast barium enema and rectosigmoidoscopy raises problems Forty-one per cent of the carcinomas were polyps with foci of invasive cancer, a diagnosis which can usually not be made by double contrast barium enema or rectosigmoidoscopy. Specificity should therefore be calculated for neoplasms, combining carcinomas and adenomas, giving a value of 99 per cent (427 of 431) The sensitivity for all neoplasms $\geqslant 1$ cm in diameter in the large bowel at the primary assessment was 94 per cent (97 of 103)

One annoying drawback of double contrast barium enema is the large number of false positive findings of diminutive polyps. In 22 patients, double contrast barium enema 'detected' 27 polyps, 23 of which were considered to be $\leqslant 1$ cm in diameter. They were all found to be false positives by repeat double contrast barium enema or by colonoscopy. This means that an 'unnecessary' assessment was performed in 18 patients, i.e. 13 per cent of those with adenomas and 28 per cent of those with adenomas $\leqslant 1$ cm in diameter according to double contrast barium enema. Considering a magnification factor of 1·3–1·4, these small 'polyps' were in reality <8 mm in diameter The cancer incidence in such small neoplasms is <1 per cent[10]. From a practical point of view, the effort needed to perform a full assessment in all patients with diminutive polyps at double contrast barium enema in screening programmes is highly questionable.

In conclusion, the sensitivity of double contrast barium enema is inadequate for this examination to be used alone in the diagnostic assessment of patients with a positive Hemoccult II test. This is particularly because of the difficulties in interpreting the films[4,9,11]. No less than seven of the 11 overlooked carcinomas could be recognized when films were reviewed. If rectosigmoidoscopy had been used alone, seven out of 29 carcinomas would have been missed. Five of these were not reached by the rectosigmoidoscope. Two carcinomas, however, were passed with the endoscope but overlooked. If double contrast barium enema had been used in combination with a rigid rectoscope seven of the ten carcinomas that had been overlooked with double contrast barium enema would have been missed. Double contrast barium enema is quite good for rectal examination but inferior in the sigmoid colon where it has to be supplemented with the flexible endoscope[4,12].

These results indicate that the combination of double contrast barium enema and rectosigmoidoscopy in the assessment of patients with a positive Hemoccult II test gives an acceptable sensitivity and that immediate retesting of those with a negative assessment is not necessary.

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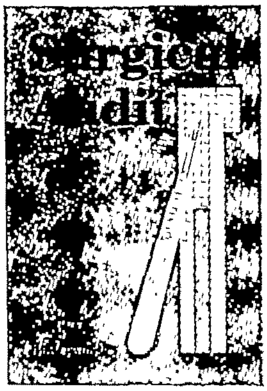

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Association of congenital hypertrophy of the retinal pigment epithelium with familial adenomatous polyposis

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Ophthalmological examinations were performed in 49 people (43 patients) from 24 families affected by familial adenomatous polyposis (FAP). No features of congenital hypertrophy of the retinal pigmented epithelium (CHRPE) were noted in six first-degree relatives without colonic polyps. Patients with Gardner's syndrome exhibited CHRPE more frequently than those without exostosis or desmoid tumour (91 per cent versus *45 per cent). In addition the prevalence of CHRPE was slightly higher in the patients with gastric or duodenal polyps (68 per cent compared with 50 per cent) in those who had a normal gastroduodenal examination. There were 11 families in which two or more patients underwent ophthalmological examinations. In five of these 11 families, all 12 patients were negative for CHRPE. In four of the remaining six families, all 11 patients had CHRPE. CHRPE is one of the pleiotropy of FAP and ophthalmological examination is an important screening test for the family of patients with CHRPE associated with FAP.*

Keywords: Congenital hypertrophy of the retinal pigment epithelium, familial adenomatous polyposis

Recent reports have described a very high incidence (from 87·5 to 100 per cent) of congenital hypertrophy of the retinal pigmented epithelium (CHRPE) in Gardner's syndrome[1–4] and familial adenomatous polyposis (FAP). They also stressed the usefulness of ophthalmological examination in family members with FAP because of the high specificity of CHRPE for FAP. Because of these reports our study was undertaken to clarify the association of CHRPE with FAP.

Patients and methods

Ophthalmological examination was carried out in 49 people from 24 FAP families including 43 patients with FAP and six first-degree relatives who to date have not been found to have colon polyps (*Figures 1* and 2). Gastroduodenal fibrescopic examination or double contrast X-ray examination of the stomach was performed in 36 of the 43 patients. Ten of 43 patients with FAP had either desmoid tumours or exostosis. In this paper these cases were defined as having the so called Gardner's syndrome. We also divided FAP patients into two groups[5], six cases of dense type and 37 cases of coarse type. The criteria for delineating these clusters were macroscopically a count exceeding 5000 total polyps, or microscopically two adenoma foci detected in a unit length (10 mm) of a histological section. Ophthalmological examinations were performed by one ophthalmologist. Following pupil dilation, the lesions were drawn on retinal maps after careful and thorough ophthalmoscopic examination. The examiner was able to detect even very small pigment lesions distributed in the peripheral part of the fundus.

Results

Three kinds of pigmented lesions were observed, each of them belonging to one of two categories, namely those with or without a halo. The three kinds of pigmented lesions observed were (a) ovoid or round lesions with a dark frame or central pigmentation, (b) ovoid or round simple dark lesions, and (c) spotty or gathered spotty dark lesions (*Figure 1*). We considered these lesions to be CHRPE. No features of CHRPE were present in the six first-degree relatives of the patients whose colon was examined and proved negative for polyps (*Figure 2*). Two of them were the parents of an FAP patient with 16 CHRPE lesions. All 28 kinds of blood types were compatible with the patient (Kindred 8). Three of the remaining cases were the siblings of patients and the other one case was the unaffected parent of a patient (Kindred 2, 3, 13).

Of 43 patients with FAP, 25 (58 per cent) had the pigmented retinal lesions. Fifteen out of 33 patients who showed no exostosis or desmoid tumour 45 per cent) had fundal lesions, compared with ten of 11 cases of Gardner's syndrome (91 per cent) who had pigmented lesions ($\chi^2 = 7{\cdot}21$, $P < 0{\cdot}01$). In 22 of 43 patients, gastric or duodenal polyps were detected. The prevalence of CHRPE in this group was 68 per cent (15/22) compared with 50 per cent (7/14) in those with neither gastric nor duodenal polyps. The prevalence of CHRPE did not differ between the dense type (3/6) and the coarse type (22/37) of polyposis patients. There were 11 families in which two or more patients underwent ophthalmological examinations. In five of these 11 families (Kindred 1, 3, 4, 5, 6) all 12 patients were negative for CHRPE. In four of the remaining six families (Kindred 10, 11, 12, 13) all 11 patients had CHRPE. In the remaining two families (Kindred 7, 9). patients with and without CHRPE were mixed in the same family.

Discussion

Chapman *et al.* observed CHRPE in all 40 FAP patients drawn from 25 pedigrees[1]. Traboulsi *et al.*[3] reported that 90·2 per cent of patients with Gardner's syndrome had pigmented lesions and that no family with documented Gardner's syndrome should be considered negative for the ocular trait before a sufficiently large number of its members had been examined. Berk *et al.*[4] also reported that 87·5 per cent of 40 FAP patients had fundal lesions. Although these findings are suggestive, Lewis *et al.*[2] reported four pedigrees with Gardner's syndrome, all of whom had normal abstract ophthalmological examinations. Our study confirmed that the patients with Gardner's manifestations had CHRPE more frequently than the patients without Gardner's manifestations, irrespective of whether they had gastroduodenal

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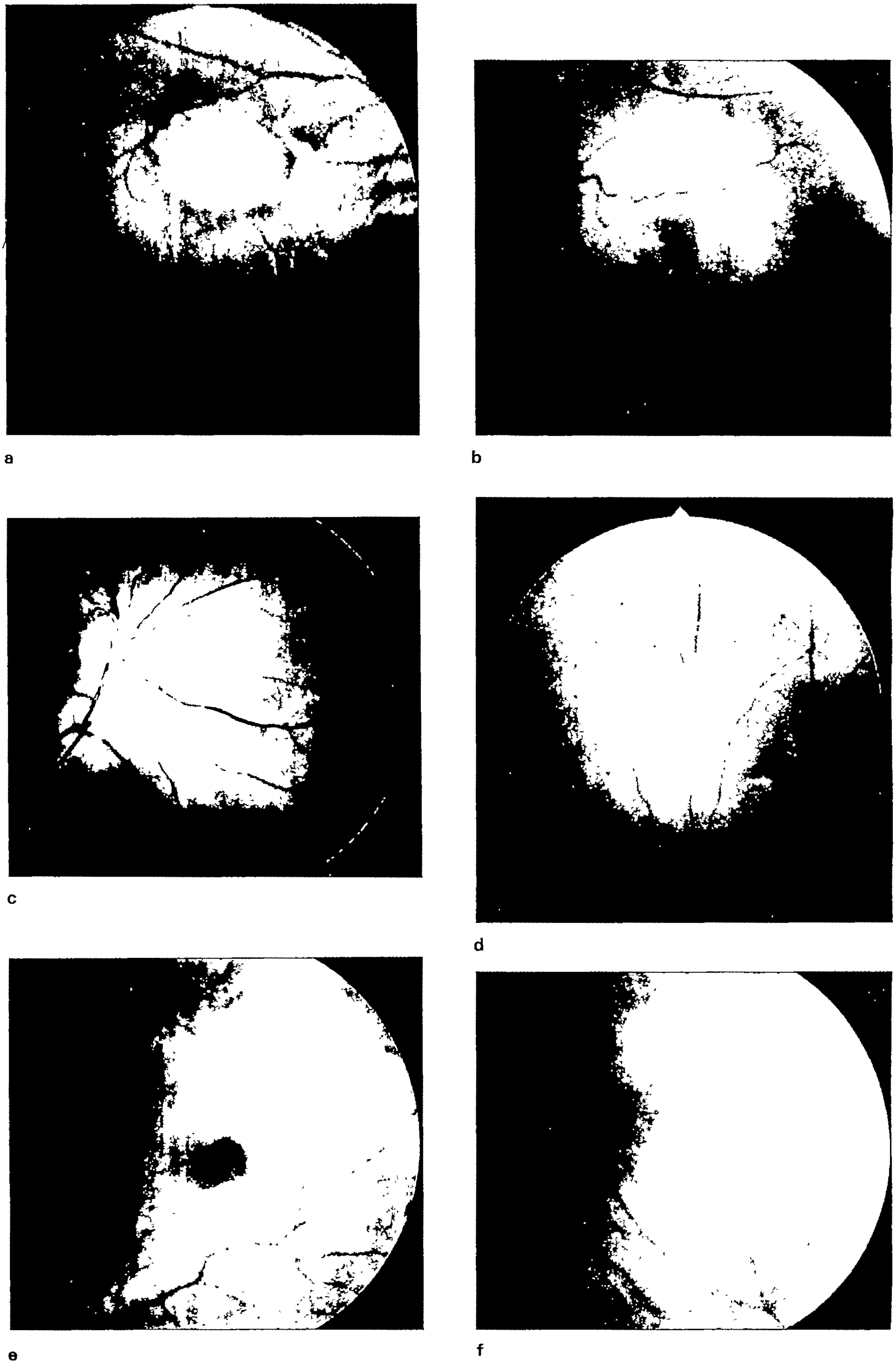

Figure 1 *Three different retinal lesions in two categories, with or without halo* **a** *with halo, dark frame or central depigmentation,* **b** *with halo, simple dark lesion;* **c** *with halo, spotty lesion,* **d** *without halo, dark frame or central depigmentation,* **e** *without halo, simple dark lesion, and* **f** *without halo, spotty lesion*

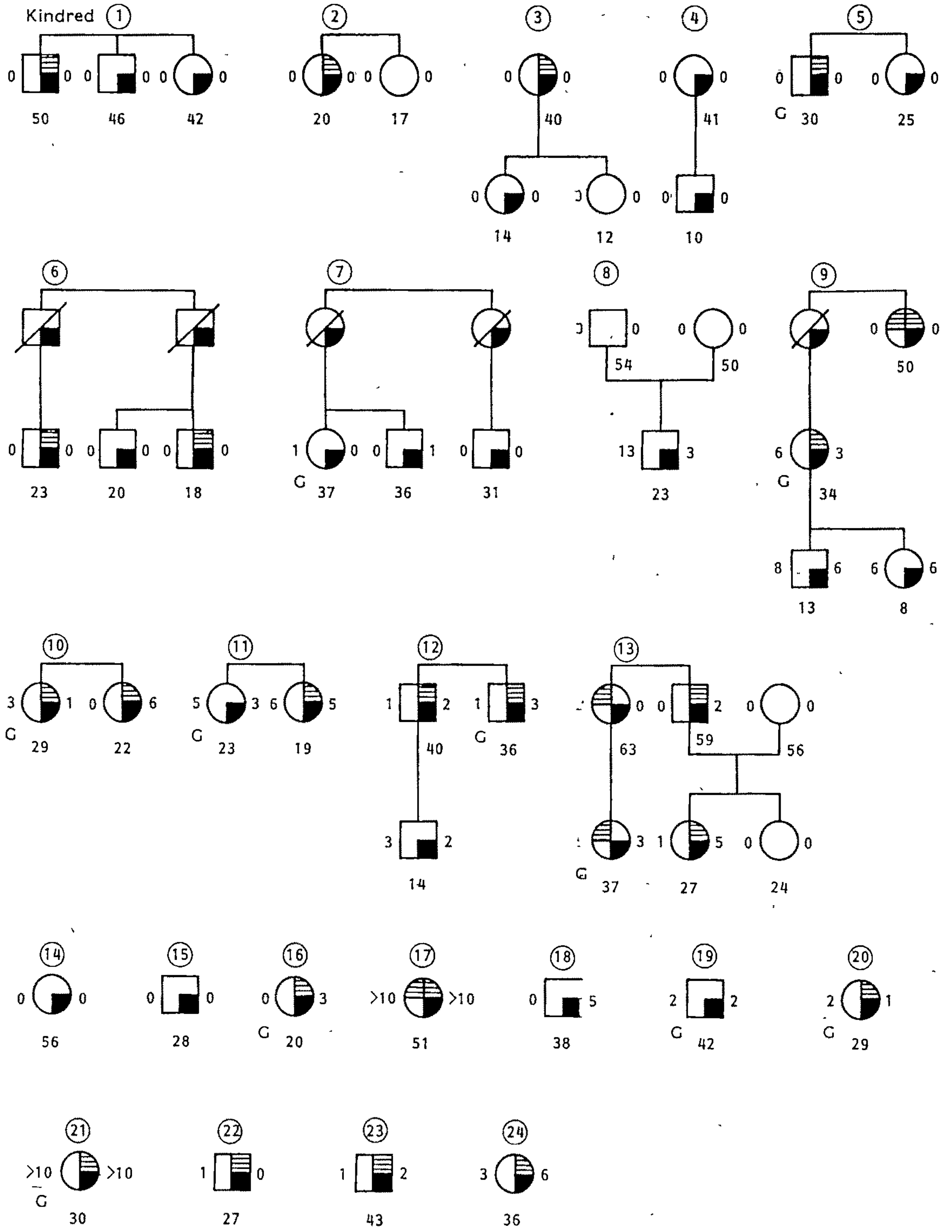

Figure 2 *Abbreviated family trees of patients of adenomatosis coli* □ 28, *a male of 28 years who was examined in the colon and polyp was negative,* ○, *a female who was examined and colonic polyp was negative,* 6◑5, *number of pigmented lesions of the retina right 6, left 5;* ◪, *polyposis of the colon,* ◑, *polyposis of the colon with colonic cancer,* ◕, *polyposis of the colon with extracolonic cancer,* G, *Gardner's syndrome, and* ☒, *deceased*

polypoid lesions. Our results also support the hypothesis that patients in the same family show similar ocular manifestations. Naylor and Lebenthal[6] stated that if members of different families are thoroughly evaluated, Gardner's patients invariably give rise to offspring who will eventually develop the full-blown syndrome while patients with established simple familial colorectal polyposis will produce offspring devoid of extracolonic manifestations, except for desmoid tumours. However, the definition of Gardner's syndrome is so obscure that it cannot be used to screen families for FAP. We found that the density of colonic polyps in patients of the same family was similar when they were over 20 years old but that the density was independent of CHRPE.

We conclude that CHRPE is one of the independent pleiotropy of FAP, as are gastric hyperplastic polyps, osteoma, desmoid tumours and difference in colonic polyp density. Because CHRPE is readily defined, ophthalmological examination is an important screening test for the family members of CHRPE positive patients.

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Faecal occult blood screening for colorectal neoplasia: a randomized trial of three days or six days of tests

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Haemoccult®, a guaiac test for faecal occult blood, detects 56–78 per cent of asymptomatic carcinomas when performed over 3 days. In patients with known colorectal cancer the sensitivity of the test for neoplasia is increased by extending the test period to 6 days. We report the first randomized comparison of 3 day with 6 day testing in asymptomatic individuals. 35 184 age and sex matched individuals were randomly allocated to receive Haemoccult over 3 or 6 days. The tests were completed by 10 176 (57·8 per cent) of the 17 616 offered 3 day Haemoccult and 9461 (53·9 per cent) of the 17 568 offered 6 day Haemoccult, a significant decrease in compliance ($P<0·001$)*. Of the 3 day Haemoccult tests 131 (1·29 per cent) were positive, significantly fewer than the 160 (1·69 per cent) positive tests after 6 day Haemoccult* ($0·01<P<0·02$)*. Investigation of subjects with a positive test revealed 20 carcinomas (1·14 per 1000 offered and 1·97 per 1000 completing the test) in the 3 day group and 24 carcinomas (1·37 per 1000 offered and 2·54 per 1000 completing the test) after 6 day Haemoccult tests* ($0·5<P<0·7$) *for those offered the test and* $0·3<P<0·5$ *for those completing it). After 3 day Haemoccult 112 adenomas in 76 persons were detected (4·31 per 1000 offered and 7·47 per 1000 completing the test). In the 6 day group 123 adenomas in 83 persons (4·72 per 1000 offered and 8·77 per 1000 completing the test) were detected* ($0·5<P<0·7$) *for those offered the test and* $0·3<P<0·5$ *for those completing it). Large adenomas were found in 27 individuals after 3 day testing (1·53 per 1000 offered the test and 2·65 per 1000 completing it) and in 35 individuals after 6 day testing (1·99 per 1000 offered the test and 3·70 per 1000 completing it)* ($0·3<P<0·5$ *for those offered the test and* $0·1<P<0·2$ *for those completing it). This study has not demonstrated a significant increase in the yield of neoplasia in asymptomatic subjects offered Haemoccult over 6 days. However there was a significant decrease in compliance and a higher rate of colonoscopy in those offered 6 day testing.*

Keywords: Colorectal carcinoma, screening, faecal occult blood

Haemoccult® (Rohm Pharma, Darmstadt, FRG), a guaiac-based test for faecal occult blood, can detect bleeding from asymptomatic large bowel neoplasia[1,2].

It is known that cancers diagnosed following the detection of faecal occult blood are generally at a less advanced pathological stage than those occurring in matched control populations[3–5].

Mass population screening for colorectal cancer based on faecal occult blood tests may provide the first significant improvement in survival from this disease in the last 30 years, although long-term survival data from the randomized controlled trials are not yet available.

Haemoccult has a low incidence of false positive reactions[6–8]. However when used for screening asymptomatic individuals the interval cancer rate (cancers presenting in the interval following a negative test and a retest) at 2 years is between 22 per cent and 44 per cent[3–5]. It is likely that the majority of these were missed by the screening test.

Colorectal cancers bleed intermittently[9], and blood is likely to be unevenly mixed in the stool. Multiple stool testing, performed over a number of days, might reduce the incidence of false negative results due to these factors and in 1971 Greegor suggested two samples from three consecutive daily bowel movements should be prepared[2]. Since then the 3 day test period has been standard in screening studies. Extension of the period to 6 days increased the yield of carcinomas detected by Haemoccult from 72·2 per cent to 90·3 per cent in patients with known colorectal cancer[10]. The aim of this study was to examine the effect of 6 day testing on the yield of neoplasia in asymptomatic individuals participating in a screening study, where the effect on compliance must also be taken into account.

Patients and methods

A trial of faecal occult blood testing for asymptomatic large bowel cancer was instituted in Nottingham in 1981. To date 123 000 participants between 50 and 74 years of age have been randomly allocated by household into a test group who were sent Haemoccult tests, or a control group. Those persons who accept the invitation to perform the tests are offered further tests at 2-yearly intervals.

Between 1986 and 1988 those in the test group were further randomized into groups invited by their general practioner to perform Haemoccult tests over 3 days or 6 days. Dietary restrictions were not

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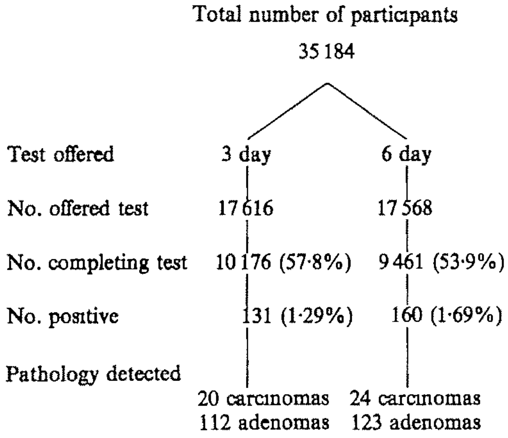

	3 day	6 day
Total number of participants	35 184	
Test offered	3 day	6 day
No. offered test	17 616	17 568
No. completing test	10 176 (57·8%)	9461 (53·9%)
No. positive	131 (1·29%)	160 (1·69%)
Pathology detected	20 carcinomas 112 adenomas	24 carcinomas 123 adenomas

Figure 1 *Yield of neoplasia for 3 day or 6 day haemoccult tests*

imposed initially; however those with positive tests were asked to repeat the test with standard dietary restrictions, avoiding red meats and vegetables with high peroxidase activity. Those who remained positive were seen in a designated early diagnosis clinic and underwent colonoscopy, supplemented by double contrast barium enema examination if the caecum was not visualized. A total of 17 616 people were offered 3 day tests and 17 568 were offered 6 day tests. We have compared the effect of extended testing on compliance, positivity rate and the detection of large bowel neoplasia (carcinoma or histologically proven adenomas) in the two groups.

Cancers were staged according to Dukes' classification to which was added a stage D for patients with distant metastases or locally unresectable disease.

Statistical comparisons have been made using the χ^2 test.

Results

A total of 35 184 individuals were entered into the test group during the trial period (*Figure 1*). Of these 17 616 were offered 3 day tests and 10 176 completed and returned the test, a compliance rate of 57·8 per cent. A further 17 568 were offered 6 day tests of whom 9461 returned completed tests, a compliance rate of 53·9 per cent, significantly lower ($P<0\cdot001$) than that obtained for 3 day testing.

Of the 10 176 completing 3 day tests, 131 (1·29 per cent) remained positive following dietary restrictions. Of the 9461 completing 6 day tests 160 (1·69 per cent) gave consistently positive results following dietary restrictions, a significant increase ($0\cdot01<P<0\cdot02$) when compared with 3 day testing.

Further investigation of those individuals with positive tests revealed 20 carcinomas in the 3 day test group and 24 carcinomas in the 6 day test group. The yield of carcinomas per 1000 offered the test and per 1000 completing the test was greater for 6 day testing than 3 day testing (1·37 *versus* 1·14 and 2·54 *versus* 1·97 respectively), although this difference did not reach statistical significance ($0\cdot3<P<0\cdot5$ for those offered the test and $0\cdot1<P<0\cdot2$ for those completing it).

In the 3 day group 27 individuals with adenomas >2 cm in size were identified, a detection rate of 1·53 per 1000 offered the test and 2·65 per 1000 completing the test. Following 6 day testing, 35 individuals with adenomas of >2 cm were identified, 1·99 per 1000 offered the test and 3·70 per 1000 completing the test. The differences observed between 3 and 6 day testing were not statistically significant ($0\cdot3<P<0\cdot5$ for those offered the test and $0\cdot1<P<0\cdot2$ for those completing it).

When all adenomas were included the difference in yield was less marked. A total of 112 adenomas in 76 individuals was detected in the 3 day group, a detection rate of 4·31 people with adenomas per 1000 offered the test and 7·47 per 1000 completing the test. In the 6 day group 123 adenomas in 83 people were detected, 4·72 people per 1000 offered the test and 8·77 per 1000 completing the test ($0\cdot5<P<0\cdot7$ for those offered the test and $0\cdot3<P<0\cdot5$ for those completing it).

Considering the subsequent detection of a carcinoma or adenoma as a true positive reaction, 35 (26·7 per cent) individuals had a false positive Haemoccult result following 3 day testing and 53 (33 per cent) following 6 day testing ($0\cdot2<P<0\cdot3$).

The predictive value of a positive test for carcinoma in the 3 day test group is 15·3 per cent and for the 6 day group it is 15·0 per cent ($P>0\cdot99$). The positive predictive value of a Haemoccult test for carcinoma or adenoma is 73·3 per cent for 3 day testing and 66·9 per cent for 6 day testing ($0\cdot2<P<0\cdot3$).

The stage, morphological characteristics and site of the carcinomas are given in *Tables 1* and *2*. There is no difference in the number of polypoidal carcinomas, and no significant difference in stage, degree of differentiation and anatomical site between the cancers detected by 3 day testing, and those detected by 6 day testing.

Discussion

It is evident that a number of large bowel cancers are not detected by Haemoccult testing, both in symptomatic[10] and asymptomatic individuals[3–5].

A reduction in the number of 'missed' cancers may be achieved by increasing the sensitivity of the test for blood; however this is likely to be accompanied by a corresponding decrease in its specificity for neoplasia. Fecatest® (Labsystems Oy, Helsinki, Finland), another guaiac-based test, has a sensitivity limit of 2–3 ml blood/day and gives consistently lower false negative results than Haemoccult[11] Unfortunately, as its sensitivity approximates to the upper limit of normal blood loss in healthy individuals, the number of false positive results may be as high as 50 per cent[12]. Such a test would be unsuitable for screening purposes.

Dehydration of the sample has been cited as a cause of false negative reactions and rehydration of the test card before development has increased the sensitivity of the test; however, this has been accompanied by an unacceptable increase in the false positive rate in a screened population and a fall in the predictive value for neoplasia[13].

The encouraging improvement in sensitivity for neoplasia achieved by 6 day testing in patients with symptomatic large bowel cancers suggested that 6 day testing would result in a similar benefit in asymptomatic individuals. Indeed the yield

Table 1 *Characteristics of cancers detected by 3 and 6 day Haemoccult*

	3 day	6 day
Stage		
A	9	10
B	5	7
C	6	7
D	0	0
Differentiation		
Well	1	3
Moderate	11	13
Poor	2	3
Unknown	6	5
Polyp cancers	5	5

Table 2 *Site of cancers detected by 3 and 6 day Haemoccult*

Site	3 day	6 day
Rectum	3	1
Rectosigmoid	5	3
Sigmoid colon	7	15
Descending colon	1	2
Transverse colon	2	1
Ascending colon	1	1
Caecum	1	1

for both carcinomas and adenomas was greater, but these differences were not statistically significant in this trial of over 35 000 screened subjects.

This may imply that the bleeding pattern in asymptomatic individuals is different from that in patients with symptomatic large bowel cancer. One might expect tumour morphology to be responsible for this; a significantly greater number of asymptomatic cancers detected in the Nottingham study are polypoidal carcinomas when compared with symptomatic carcinomas in the control group[3] and Farrands and Hardcastle[10] found that polypoidal cancers resulted in fewer positive 3 day tests than ulcerated tumours (85 per cent *versus* 65 per cent) However this difference was not statistically significant, and in the present study there was no significant difference in the proportion of tumours that were polypoidal in the 3 and 6 day groups.

In symptomatic patients a significantly greater number of well differentiated tumours are Haemoccult negative compared with the moderately and poorly differentiated growths[10]. The proportion of well and moderately differentiated cancers detected in asymptomatic individuals is higher than the proportion seen in a matched control population[3] and this may contribute to the failure of 6 day testing to increase yield in asymptomatic individuals.

Acceptability of the test is of fundamental importance to the success of a screening study. Significantly fewer people found 6 day testing acceptable; this deterioration in compliance will limit the role of 6 day testing in screening programmes

The increased yield of neoplasia in relation to the number of people offered the test might be expected to become significant had compliance not been affected. However we have also calculated yield in terms of numbers completing and returning the tests, a calculation independent of compliance, and there remains no statistical difference in yield for either carcinoma or adenoma.

Accepting that the yield of both carcinomas and adenomas was greater in the 6 day group, one might expect the difference to demonstrate statistical significance if compared in a study involving larger numbers of participants However it is also possible that the rate of false positive reactions (with the associated rise of iatrogenic injury at colonoscopy) would increase accordingly.

An evaluation of which days subjects offered 6 day testing are positive will provide further information relating to the value of screening over 6 days. Such a trial is now being undertaken. From the present study we may conclude that the benefit of extended testing in screened subjects is not as clear cut as in patients with known colorectal cancer and that, at the present time, 3 day Haemoccult should be used for screening purposes.

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Prospective study of colorectal cancer in the West of Scotland: 10-year follow-up

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Six hundred and forty-five patients presenting with colorectal cancer over a 6-year period were studied prospectively. At the time of presentation almost half the patients had clinical evidence of local tumour fixity and over one-quarter had distant metastases. The overall resectability rate was 70·8 per cent, apparently curative resection being obtained in 52·5 per cent. Overall operative mortality rate was 13·8 per cent, increasing in the elderly. Approximately 70 per cent of patients undergoing 'curative' resections survived for 2 years, 50 per cent survived for 5 years and 40 per cent survived for 10 years. After palliative resection approximately 10 per cent of patients survived for 5 years; only six of 133 patients (4 per cent) undergoing palliative diversion survived for 2 years. This prospective study confirms the advanced stage of colorectal cancer as it presents to a non-specialist centre. Although the poor outlook is largely a consequence of the advanced nature of the disease, there is evidence to suggest that the results of surgical intervention could be improved.

Keywords: Colorectal cancer, prospective, follow-up

Colorectal cancer is the second most common malignancy in the Western world. Almost 27 500 new cases are registered in the UK each year[1]. There is considerable variation in survival rates amongst centres; retrospective population-based studies show that only 30 per cent of patients survive for 5 years[2–9] while reports from specialist centres suggest that higher salvage rates can be achieved[10–13].

To exclude the potential bias inherent in retrospective studies, in 1974 a prospective study of all patients presenting with colorectal cancer in a geographically defined population in the Eastern District of Glasgow was initiated.

Patients and methods

All patients presenting to the Royal Infirmary, Glasgow between 1 January 1974 and 31 December 1979 with a clinical diagnosis of colorectal cancer were included in the study. The management of these patients was supervised by 12 consultant general surgeons, none of whom had a specific interest in colorectal surgery. Data recorded prospectively included age, sex, site of cancer, the nature of surgery and postoperative mortality. Tumours were classified according to site; lesions of the caecum, ascending colon and hepatic flexure were classified as right-sided lesions, whereas lesions of the transverse colon, splenic flexure and descending colon were classified as left-sided lesions This classification is based on that adopted by the NSABP study group[14]. Carcinomas arising at the rectosigmoid junction were classified as rectal cancers. The extent of tumour spread was assessed by conventional Dukes' classification based on histological examination of the resected specimen[15]

The patients were deemed to have had a 'curative' resection if the surgeon considered that there was no macroscopic residual tumour once resection had been completed Patients in whom resection was carried out in the presence of distant metastases or in whom inadequate local clearance was achieved were deemed to have had a 'palliative' resection. Patients in the 'palliative diversion' group were treated by proximal defunctioning colostomy or by-pass, the primary tumour being left *in situ*. In a few patients surgical intervention was deemed inappropriate or laparotomy only was performed.

All patients were followed at 3-monthly intervals for 2 years at a designated colorectal cancer clinic, 6-monthly for a further 3 years and thereafter annually until the tenth anniversary or death The dates of first detected recurrence and death were recorded Percentage survival was estimated using standard life table estimates and statistical comparisons were made using the log rank test[16]

Results

Six hundred and forty-five patients were included in the study, of whom 23 per cent were admitted as an emergency and 56 per cent were 65 years or older with the peak incidence between 65 and 74 years (*Table 1*). The commonest sites of the primary tumour were the rectum followed by sigmoid colon and caecum. More women had colon cancer mainly owing to an excess of women aged between 45 and 54 years and over 75 years; more men had rectal cancer mainly due to an excess of men aged between 55 and 64 years. For men the colon:rectum ratio was 1·4:1, whereas for women the ratio was 2·5:1.

The relationship between the site of tumour and the extent of disease is shown in *Table 2*. In almost 45 per cent of patients there

Table 1 *Age, sex and tumour site of 638 patients* with colorectal cancer*

Tumour site	Age (years)					Total	
	≤45	45–54	55–64	65–74	75+	Male	Female
Right	3	15	32	47	31	52	76
Left	7	15	30	37	23	53	59
Sigmoid	2	30	46	53	40	75	96
Rectum	7	38	55	80	47	133	94
Total	19 (3·0)	98 (15·4)	163 (25·5)	217 (34·0)	141 (22·1)	313	325

* Details of seven patients who had multiple tumours or widespread intra-abdominal metastases with no obvious primary were not included in this analysis. Values in parentheses are percentages

Table 2 *Relationship between tumour site and extent of disease*

Tumour site	No spread	Local	Distant	Local and distant	Not known	Total
Right	63	25	16	20	4	128
Left	43	29	17	21	2	112
Sigmoid	65	55	18	32	1	171
Rectum	109	49	9	45	15	227
Total	280 (43·9)	158 (24·8)	60 (9·4)	118 (18·5)	22 (3·4)	638

Values in parentheses are percentages

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Table 3 *Relationship between tumour site and resectability*

Tumour site	Curative resection	Palliative resection	Palliative diversion	Laparotomy only	Total
Right	69	24	25	10	128
Left	56	22	22	12	112
Sigmoid	86	36	39	10	171
Rectum	124	35	47	21	227
Total	335 (52·5)	117 (18·3)	133 (20·8)	53 (8·3)	638

Values in parentheses are percentages

Table 4 *Relationship between age, resectability and operative mortality*

Operative procedure	Age (years)					
	<45	45–54	55–64	65–74	75+	Total
Curative resection	14	49	91	117	64	335
Palliative resection	3	25	37	35	17	117
Palliative diversion	1	14	28	46	44	133
Laparotomy only	1	10	6	19	17	53
Operative mortality	1 (5·3)	8 (8·2)	19 (11·7)	31 (14·3)	29 (20·4)	88 (13·8)

Values in parentheses are percentages

was clinical evidence of local tumour fixation; over 25 per cent had distant metastases at the time of presentation.

The relationship between tumour site and resectability is shown in *Table 3*. The overall resectability rate was 70·8 per cent, of these 52·5 per cent were regarded as curative and 18·3 per cent as palliative. Palliative diversion was performed in 20·8 per cent of patients and 8·3 per cent underwent laparotomy only or had no surgical treatment. There was no difference between men and women in terms of resectability. Of the 335 patients undergoing curative resection, 18 (5·4 per cent) had Dukes' A tumours, 177 (52.8 per cent) had Dukes' B and 140 (41.8 per cent) had Dukes' C tumours.

The relationship between age, resectability and operative mortality is shown in *Table 4*. The curative resection rate was highest in patients younger than 45 years and lowest in those aged 75 years or older. The overall operative mortality rate was 13·8 per cent being 6·2 per cent for curative resection, 14·2 per cent for palliative resection, 25 per cent for palliative diversion and 58 per cent for laparotomy alone. Operative mortality increased to over 20 per cent in patients aged 75 years or older.

The disease-related mortality figures for curative resection and palliative resection are shown in *Table 5*. Twenty-three (3 per cent) patients have been lost to follow-up; the median follow-up time is 12 years. Approximately 70 per cent of patients survived for 2 years following curative resection, 50 per cent survived for 5 years and 40 per cent survived for 10 years. Of the patients with Dukes' A tumours undergoing curative resection, 81 per cent survived for 5 years compared with 56 per cent of Dukes' B and 33 per cent of Dukes' C patients. One in five patients undergoing palliative resection survived for 2 years, and one in ten survived for 5 years; median survival was 11 months. All but six of the 133 patients undergoing palliative diversion died within 2 years; the median survival time was 6 months. There was no statistically significant difference in survival between men and women for either colon or rectal cancer.

Discussion

Variations in reported outcome following surgery for colorectal cancer may be due to the inaccuracies inherent in retrospective studies, differences in the patient population studied, the analysis of results or surgical expertise.

The results of the present prospective study of patients presenting with colorectal cancer within a defined geographical area are similar to previous retrospective population-based studies and confirm the low resectability rate (70 per cent), high operative mortality rate (13·8 per cent) and poor 5-year survival rate (27 per cent) achieved in routine surgical practice.

The majority of patients in this study presented late, 23 per cent as an emergency, almost 45 per cent with local fixity and over 25 per cent with metastatic disease. Various authors[4,5] have commented on the preponderance of poor risk patients in population studies and the relative selectivity of specialist centres, suggesting that stage for stage the survival following surgery is not dissimilar.

Furthermore, comparisons amongst centres are complicated by varying methods of analysing outcome after surgery. These differences have been highlighted by Schofield and his colleagues who, using different methods to analyse the same database, showed that the 3-year survival rate varied from 43 per cent (crude tumour-free survival of all patients) to 82 per cent (age-corrected survival for patients surviving curative resection) depending on the method used[17]. In this study, the 10-year survival rate varied from 16 per cent (crude survival) to 44 percent (disease-related survival of patients surviving surgery) (*Table 6*).

While the high incidence of patients with locally advanced or metastatic disease is likely to contribute to the poorer results achieved, the possibility that the level of surgery performed is suboptimal should be considered. Clearly patients who present with disseminated disease are not amenable to cure. In the remaining patients the importance of achieving adequate local control of the disease cannot be over-emphasized. Quirke and his colleagues demonstrated that local recurrence following apparently curative resection was due to the presence of occult lateral tumour spread[18], a situation analogous to the development of liver secondaries from occult hepatic metastases undetected at the time of laparotomy[19]. In a recent multicentric study, although the overall local recurrence rate was 14 per cent, it varied from <5 per cent to >20 per cent amonst individual

Table 5 *Relationship between operative procedure and survival*

Tumour site	Patients surviving (%)				
	Curative resection (years)			Palliative resection (years)	
	2	5	10	2	5
Right	66	50	42	18	9
Left	77	42	39	27	16
Sigmoid	71	45	39	15	6
Rectum	73	49	42	19	6
Mean	71	47	41	19	9

Table 6 *Ten-year survival rates using different measures of survival*

Patients	Measure	Ten-year survival rate (%)
All cases (*n* = 645)	Total mortality	16
	Disease related	23
All resections (*n* = 458)	Total mortality	23
	Disease related	31
Curative resections (*n* = 338)	Total mortality	30
	Disease related	41
Curative resections excluding postoperative deaths (*n* = 317)	Disease related	44

surgeons suggesting that in the latter the extent of excision was inadequate[20] In this study the overall local recurrence rate following apparently curative resection was 10·9 per cent, ranging from zero to 21 per cent amongst individual surgeons.

The low resectability rate suggests a conservative approach There was evidence that resection was not attempted in the presence of tumour adherence, particularly in the rectum and in the elderly. Almost certainly in some of these patients the tumour adherence would be due to inflammatory reaction rather than tumour infiltration and wide excision can lead to survival not substantially different from tumours of the same stage without fixation[21]. Although an increase in the number of resections might increase postoperative mortality, the quality of life of those who survive surgery would be substantially improved.

In conclusion, this prospective study in an unselected population underlines the poor results obtained by general surgeons undertaking colorectal cancer surgery. It emphasizes the advanced nature of the disease at the time of presentation; few patients presented with a Dukes' A lesion and many had evidence of disseminated disease or local tumour fixity at the time of presentation Failure to achieve adequate local control of the disease and the reluctance to undertake resection, especially in the elderly, may have contributed to the poor results. It lends further support to the contention that colorectal cancer surgery should be undertaken by surgeons with a specific interest in the disease[22,23].

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Meta-analysis of randomized, controlled clinical trials of antibiotic prophylaxis in biliary tract surgery

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In this study all available clinical trials of antibiotic prophylaxis in biliary tract surgery, published from 1965 to 1988, were examined. Results of 42 randomized, controlled trials (4129 patients), in which a group of patients treated with antibiotics was compared with a group of patients not treated with antibiotics, were pooled. Wound infection rates in the control groups range from 3 to 47 per cent and are 15 per cent overall. The overall difference in infection rates is 9 per cent in favour of antibiotic treatment (95 per cent confidence interval 7–11 per cent), while the common odds ratio is 0·30 (95 per cent confidence interval 0·23–0·38). Subgroup meta-analysis showed a significant stronger protective effect in high risk patients, while the timing of wound inspection (i.e. early in hospital or late at follow-up) markedly influenced the treatment effect reported. Comparison of wound infection rates in patients treated with first generation versus *second or third generation cephalosporins (11 trials, 1128 patients), as well as single-dose* versus *multiple-dose regimens (15 trials, 1226 patients) did not reveal any significant effect* ($P > 0{\cdot}05$) *in each trial separately as well as in the overall comparison. The results indicate that there is evidence against further use of no-treatment controls and that the choice of treatment regimen can largely be made on the basis of cost.*

Keywords: Meta-analysis, antibiotic prophylaxis, biliary tract surgery

Results of many controlled clinical trials seem to provide clear answers to the value of antibiotic prophylaxis in biliary tract surgery(Appendix A: 2a,10a,11a,16a,21a,22a,32a,33a,35a). However, some studies did not show any statistically significant difference in wound infection rates between treatment and control groups(Appendix A: 8a,12a,24a,39a) so that there are conflicting results concerning the effectiveness of prophylaxis in biliary surgery.

Experimental animal studies have demonstrated the relationship between timing of antimicrobial administration and its prophylactic efficacy[1,2]. In one prospective, clinical trial(Appendix A: 36a) it was demonstrated that antibiotic prophylaxis reduces the risk of postoperative infection after biliary tract operations if begun before operation. The experimental and clinical studies showed that effective systemic antibiotic prophylaxis requires that the antibiotic is present in the tissue at the time that contamination occurs[3]. Several other aspects of antibiotic prophylaxis are still the subject of debate. Although another animal model showed the efficacy of single-dose prophylaxis[4], clinical studies have not provided definite answers(Appendix A: 20a,23a,29a,37a,45a,46a,58a).

Additionally, reviews of reported prophylaxis studies have identified important methodological problems that question the published conclusions[5–11]. Guglielmo *et al.*[10] included biliary tract operations in their review and concluded on the basis of ten studies that antibiotic prophylaxis in biliary tract surgery reduces the incidence of wound infection only in high risk patients.

The sample size of randomized, controlled clinical trials is one of the most important reasons for controversy in antibiotic prophylaxis. Usually trials are too small to detect clinically important differences. The optimal duration of prophylaxis, the value of the newer generation cephalosporins, and the effectiveness of prophylaxis in low risk patients are other subjects of debate[1,2–16]. We decided to perform a systematic overview, also called a meta-analysis[17–23], because pooling the data from many trials might overcome the problem of small sample sizes of individual trials and give a more precise estimate of the effectiveness of antibiotic prophylaxis. Looking at subgroups by meta-analysis might solve some of the controversial problems. Therefore, consideration included the following subgroups: single dosage *versus* multiple dosage, low risk *versus* high risk, and first generation *versus* second and third generation cephalosporins.

We also examined whether inadequacies of the trials analysed had any impact on the final outcome. This was determined by use of a scoring system designed to assess the quality of randomized, controlled clinical trials[24].

Methods

Definitions

Biliary tract operations. All operations on the gallbladder and/or common bile duct, including cholecystectomy, exploration of the common bile duct and choledochoenterostomy were included.

Wound infection. There is a wide variation in the definition of wound infection in the analysed trials and sometimes no definition is given at all. Discharge of pus from the wound was most commonly used. Purulent exudate from the wound and non-purulent exudate that yielded pathogens on culture was used by others. We have classified wound sepsis into major and minor infections. Wound infection was considered major if there was discharge of pus irrespective of culture results. Redness and wound edge necrosis were considered minor infections if there was no constitutional disturbance or delay in the patient's recovery.

High risk patients. All patients meeting one or more of the following ten criteria were included: (a) acute cholecystitis within 4 weeks of surgery; (b) emergency cholecystectomy, (c) common duct stone or

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ductal exploration; (d) jaundice at the time of surgery, (e) age over 60 years; (f) previous biliary tract surgery; (g) morbid obesity; (h) non-visualization of the gallbladder on oral cholecystography, (i) diabetes mellitus, and (j) concomitant alimentary procedures

Selection of trials

Because randomization is necessary to avoid selection bias, this overview was restricted to randomized, controlled trials of prophylaxis in biliary tract surgery. Randomization between two or more treatment groups, and between one or more treatment group and a control group, were both allowed. If a study consisted of more than two treatment arms, only two were used in the analysis

All randomized clinical trials of biliary tract surgery alone or of general and gastrointestinal surgery (if biliary tract operations were specified and analysed separately) which met the following criteria were included: (a) published between 1965 and 1988; (b) antimicrobials were given to prevent infection (prophylaxis); and (c) wound infection was one of the end-points. If data on the same set of patients were published more than once, only one study was included.

An extensive search has been carried out using literature databases, *Current Contents*, reference lists, review articles and proceedings of international congresses.

The initial search was performed by a computer-assisted examination throughout 1988 of two literature databases, MEDLINE and MEDLARS-2 (Deutsches Institut für medizinische Dokumentation und Information, FRG) References were retrieved by the following keywords biliary surgery, cholecystectomy, prospective, randomized trial and prophylaxis. A manual search of *Current Contents* (1985–1988) was performed using the following keywords: biliary, biliary tract, cholecystectomy, clinical trial, prophylactic, prophylaxis, prospective, prospective study and randomized. The reference list of each retrieved report was scanned for potential eligible studies. Review articles were consulted. Because there is a tendency not to publish 'negative' trials, we also looked for unpublished studies in proceedings of international congresses on chemotherapy.

Only trials with comparable treatment arms can be pooled. If possible, we classified each trial into one of the three following groups (in each group a different comparison of treatments was studied). treatment regimen *versus* control or placebo (group I), treatment with first generation cephalosporins *versus* treatment with second or third generation cephalosporins (group II); and single-dose *versus* multiple-dose regimen (group III). Most of the trials could be classified in this manner.

Statistical methods

For each of the three groups of trials a meta-analysis was performed using the percentage of wound infection as an end-point We distinguished two different measures for assessment of differences in effect between treatment regimens. First, we calculated the differences in percentage wound infection (treatment minus control in group I trials, first minus second or third generation cephalosporins in group II trials; and single-dose minus multiple-dose administration in group III trials). Secondly, the odds ratio was computed for each trial In the group I trials this is the ratio of the odds of the presence of wound infection in the treated group to the odds of the presence of wound infection in the control group. An odds ratio equal to one indicates no effect of treatment, a ratio of less than one means a beneficial treatment effect, a ratio greater than one means a harmful treatment effect. The odds ratio was similarly defined in the group II trials (a ratio of less than one means a preference for first generation cephalosporins) and in the group III trials (a ratio of less than one means a preference for single-dose administration) Besides the estimates of percentage differences and odds ratios, 95 per cent confidence intervals were computed for each trial separately, while a common percentage difference (with 95 per cent confidence interval) and a common odds ratio (with 95 per cent confidence interval) were estimated using the methods described by DerSimonian and Laird[25] Estimates and confidence intervals for the odds ratios were graphically displayed on a log scale[26]. A test of homogeneity of both percentage differences and odds ratios was performed using the method also described by DerSimonian and Laird[25].

In the group I trials several factors were studied which might explain the heterogeneity of treatment effect differences We used linear regression analysis for the percentage differences and logistic regression for the odds ratios. On the basis of these results subgroups of trials were formed for which common effect estimates were calculated.

Criteria for subgroup meta-analysis

We studied whether the treatment effects in the group I trials (treatment *versus* control) differed in relation to one of the following six criteria. (1) route of administration of the prophylaxis (intravenous, intramuscular, local or combination); (2) the use of single or multiple doses, (3) the definition of wound infection, major *versus* minor plus major; (4) the moment of wound inspection, i.e in hospital or during follow-up, (5) first *versus* second or third generation cephalosporins; and (6) administration of the treatment in 'high' or 'low' risk patients. A trial was classified as high risk when at least 50 per cent of the patients in the trial were high risk patients. Trials not classified as high risk were considered low risk

Assessment of study quality

For assessing the quality of randomized, controlled trials we used a scoring system (*Table 1*) based on that of Chalmers *et al.*[27] and modified by Evans and Pollock[24] Basically it is a checklist of 31 questions: 15 are about design and conduct of the trial, eight are about analysis and eight are about presentation Quality scores ranging from zero to 100 were given to each study The quality assessment of the first ten studies was performed by two reviewers and the outcomes were compared. When questions were poorly defined it was difficult to answer 'yes' or 'no', and different interpretations had a remarkable influence on the outcome. After postulating special criteria for those questions we were able to obtain identical results from the two reviewers The remaining trials were then scored by only one reviewer (W.S.M) Details of the special criteria used for this scoring system are available from the authors.

Results

All 78 retrieved trials, which were eligible according to the criteria described above, are listed in the appendices. From

Table 1 *Scores for design and conduct, analysis, and presentation of reports of clinical trials*

	Yes	No
Design and conduct		
Is the sample defined?	2	0
Are exclusions specified?	2	0
Are known risk factors recorded?	3	0
Are therapeutic regimens defined?	5	0
Is the experimental regimen appropriate?	5	0
Is the control regimen appropriate?	5	0
Were appropriate investigations carried out?	2	0
Are endpoints defined?	5	0
Are endpoints appropriate?	5	0
Have numbers required been calculated?	2	0
Was patient's consent sought?	1	0
Was the randomization blind?	3	0
Was the assessment blind?	4	0
Were additional treatments recorded?	4	0
Were side-effects recorded?	2	0
Analysis		
Withdrawals		
Are they listed?	3	0
Is their fate recorded?	4	0
Are there fewer than 10 per cent?	4	0
Is there a comparability table?	3	0
Are risk factors stratified?	3	0
Is the statistical analysis of proportions correct?	3	0
Is the statistical analysis of numbers correct?	3	0
Are confidence intervals reported?	2	0
Are values of both test statistic and probability given?	1	0
In negative trials is the type II error considered?	4	0
Presentation		
Is the title accurate?	2	0
Is the abstract accurate and helpful?	3	0
Are the methods reproducible?	3	0
Are the sections clear-cut?	2	0
Can the raw data be discerned?	2	0
Are the results credible?	3	0
Do the results justify the conclusions?	3	0
Are the references correct?	2	0
Total	100	0

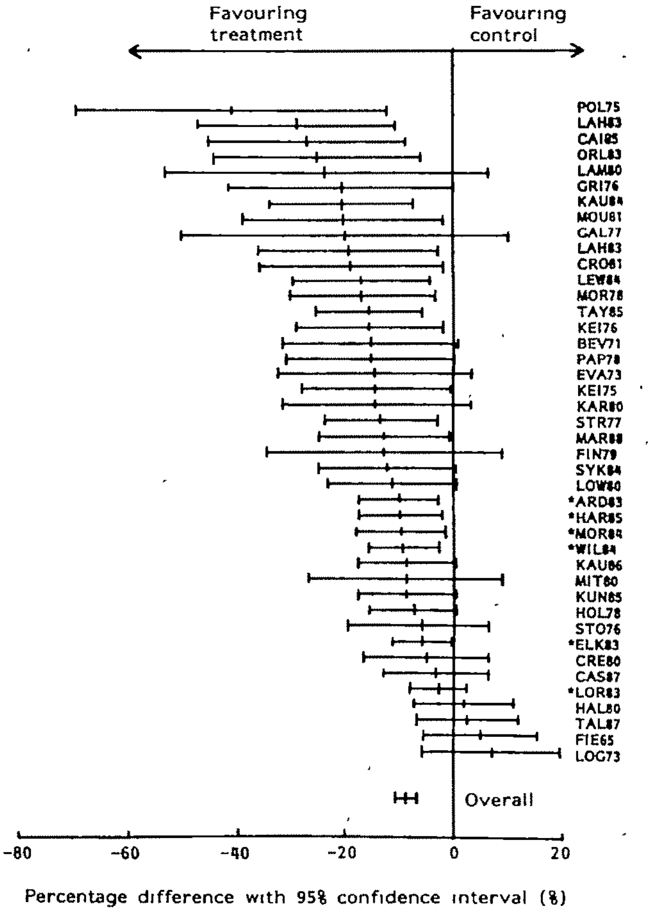

Figure 1 *Percentage differences with 95 per cent confidence intervals for 42 trials comparing treatment* versus *control and common 95 per cent confidence interval * Most informative trials, i.e. those with the smallest confidence intervals*

these trials 18$^{\text{(Appendix B 1b–18b)}}$ have been withdrawn for various reasons: (1) study not eligible for one of the three groups of meta-analysis$^{\text{(Appendix B 1b–15b)}}$; (2) sample size less than ten$^{\text{(Appendix B 16b)}}$; and (3) abstract with incomplete data$^{\text{(Appendix B 17b,18b)}}$. Sixty studies accepted for meta-analysis were divided into three groups depending on randomization (some studies with more than two treatment arms could be classified in more than one group):

I Treatment regimen *versus* control or placebo (42 trials)$^{\text{(Appendix A 1a–41a)}}$;

II First generation cephalosporins *versus* second or third generation drugs (11 trials)$^{\text{(Appendix A 42a–52a)}}$;

III Single-dose *versus* multiple-dose regimen (15 trials)$^{\text{(Appendix A 3a,5a,9a,37a,46a,51a,53a–60a)}}$.

Group I trials

The overall percentage difference between wound infection in the treated group and wound infection in the control group is 9 per cent in favour of antibiotic treatment (95 per cent confidence interval 7–11 per cent; *Figure 1*). The corresponding results for the odds ratios (*Figure 2*) is 0·30 in favour of antibiotic treatment (95 per cent confidence interval 0·23–0·38). In terms of percentage differences the test revealed significant heterogeneity ($P<0·005$) in contrast to the odds ratios ($P>0·10$).

In the subgroup analyses of the group I trials only two factors appeared to have a significant effect on the percentage differences: (a) high risk (administration of the treatment in high or low risk patients) and (b) inspection time (the moment of wound inspection, in hospital or during follow-up). Therefore, we formed four subgroups: (1) low risk patients with early (in hospital) wound inspection; (2) low risk patients with late (follow-up) wound inspection, (3) high risk patients with early wound inspection; and (4) high risk patients with late wound inspection. Common estimates and 95 per cent confidence intervals were calculated within each subgroup for the percentage differences (*Figure 3*) and the odds ratios (*Figure 4*). The percentage differences were respectively 8, 10, 13 and 25 per cent.

Assessment of study quality

None of the items that score study quality was associated with the heterogeneity in percentage differences. The distribution of the quality sum-scores for design and conduct, analysis, presentation, and overall score (maximum values of 50, 30, 20 and 100 respectively) of the 40 papers (42 trials) from group I are shown in *Table 2*.

Group II trials

Percentage differences and odds ratios for the 11 trials in group II (first generation *versus* second or third generation cephalosporins) did not reveal any significant differences. The common percentage difference is 0·5 per cent in favour of the newer generation (95 per cent confidence interval from −1·5 to +2·5 per cent; *Figure 5*); the common odds ratio is 1·18 in favour of the newer generation (95 per cent confidence interval 0·69–2·00; *Figure 6*).

Group III trials

From the 15 group III trials (single-dose *versus* multiple-dose regimen) we also could not detect any significant difference. Here, the common percentage difference is 0·4 per cent favouring single-dose therapy (95 per cent confidence interval

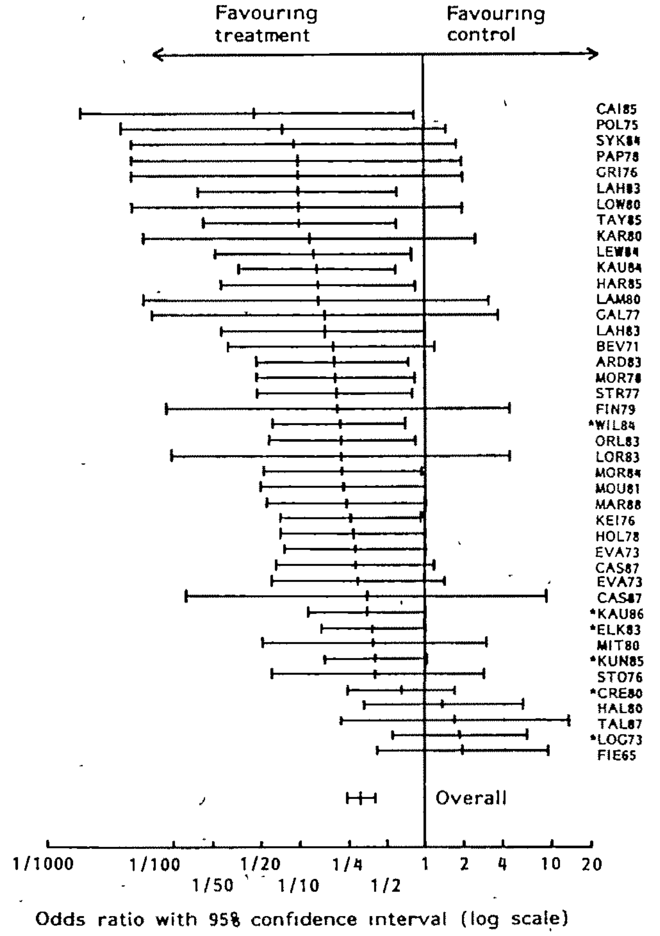

Figure 2 *Odds ratios with 95 per cent confidence intervals (log scale) for 42 trials comparing treatment* versus *control and common 95 per cent confidence interval * Most informative trials, i.e. those with the smallest confidence intervals*

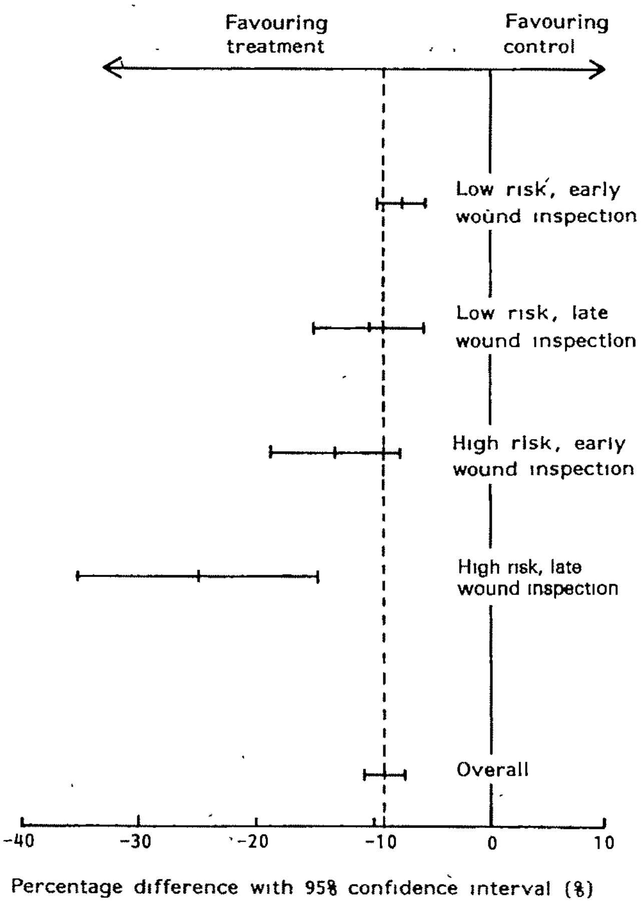

Figure 3 *Common percentage differences with 95 per cent confidence intervals for four subgroups of 42 trials comparing treatment* versus *control*

from −1·1 to +1·9 per cent; *Figure 7*), while the common odds ratio is 0·80 favouring single-dose therapy (95 per cent confidence interval from 0·41 to 1·57; *Figure 8*).

Discussion

Although wound infections are not common after cholecystectomy (rates of 2–20 per cent are quoted in the literature), improvement is still a worthwhile aim because cholecystectomy is one of the most common operations on the digestive system. Many controlled clinical trials have been performed to show the effectiveness of prophylactic antimicrobials, or to show whether one treatment is better than another. Individually, most trials are too small to detect small differences with sufficient statistical power. If we assume a 15 per cent infection rate without treatment, the expected infection rate with antibiotic prophylaxis is approximately 6 per cent since we showed a 9 per cent overall difference. To demonstrate that such a difference is statistically significant (with a 90 per cent power and use of one-sided testing, $\alpha = 0{\cdot}05$) it is necessary to study a total of at least 350 patients. The size of the largest study in this meta-analysis was 330 patients[Appendix A 6a].

To obtain a stable estimate of the effect of prophylactic antibiotics and more reliable answers to several subjects of debate, such as single-dose prophylaxis and the use of newer cephalosporins, we have performed this meta-analysis.

Only prospective randomized trials were included in the analysis to overcome selection bias Results of trials with pooled data from all kinds of general or gastrointestinal operations may be different from those of biliary tract surgery alone Therefore, only biliary tract operations have been included in this meta-analysis. To avoid publication bias as much as possible, we decided to include all trials that we could retrieve, including abstracts from proceedings of international congresses. Trials with a sample size of less than ten were withdrawn from analysis. Because of study heterogeneity, included trials have been divided into three groups. (I) treatment *versus* no-treatment control; (II) first generation *versus* second or third generation cephalosporins; and (III) single-dose *versus* multiple-dose regimens.

For assessment of the effectiveness of antibiotic prophylaxis we used two different measures: the difference in percentage wound infection and the odds ratio. Although the odds ratio has certain favourable mathematical properties, the difference in percentages is easier to interpret The data did not show a preference for one of these measures, and generally both measures led to the same results, with the exception of the test for homogeneity in the group I trials. We found a 9 per cent difference in wound infection percentage, favouring antibiotic treatment *versus* controls. The demonstrated effectiveness of prophylaxis in biliary tract surgery is evidence against further use of no-treatment controls. Future trials should be performed *versus* a proven prophylactic regimen, for instance a first generation cephalosporin.

Besides the effectiveness of antibiotic prophylaxis we found a stronger protective effect in high risk patients. In addition, the timing of wound inspection had an important influence on treatment effect. Late (follow-up) wound inspection showed a higher infection rate than early (in hospital) wound inspection. Percentage differences in the four subgroups (low risk, early

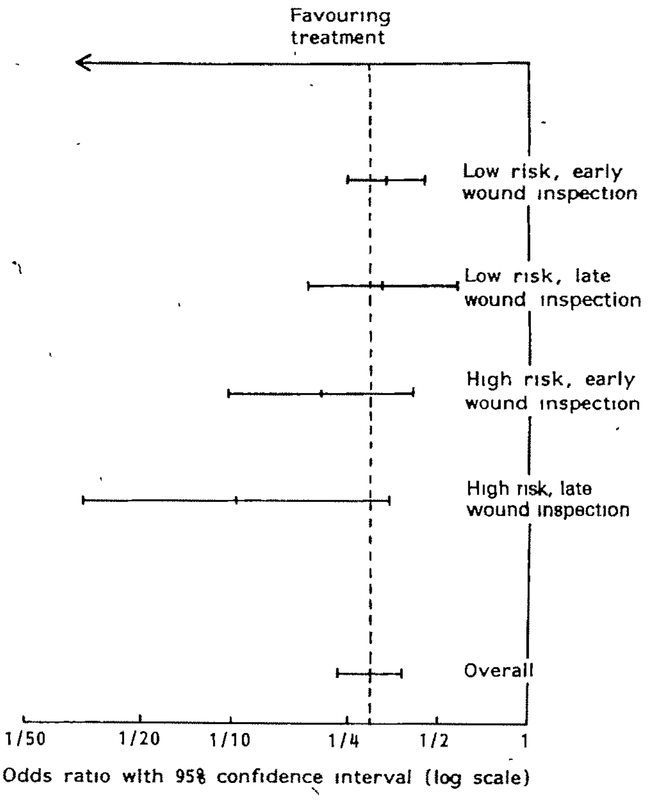

Figure 4 *Common odds ratios with 95 per cent confidence intervals (log scale) for four subgroups of 42 trials comparing treatment* versus *control*

Table 2 *Distribution of scores as specified in Table 1 for 40 reports of 42 trials comparing treatment* versus *control*

	Range	Mean(s.d.)
Design and conduct	17–42	29·0(5·9)
Analysis	4–21	10·2(3·5)
Presentation	2–17	9·2(3·3)
Overall score	34–66	48·5(7·9)

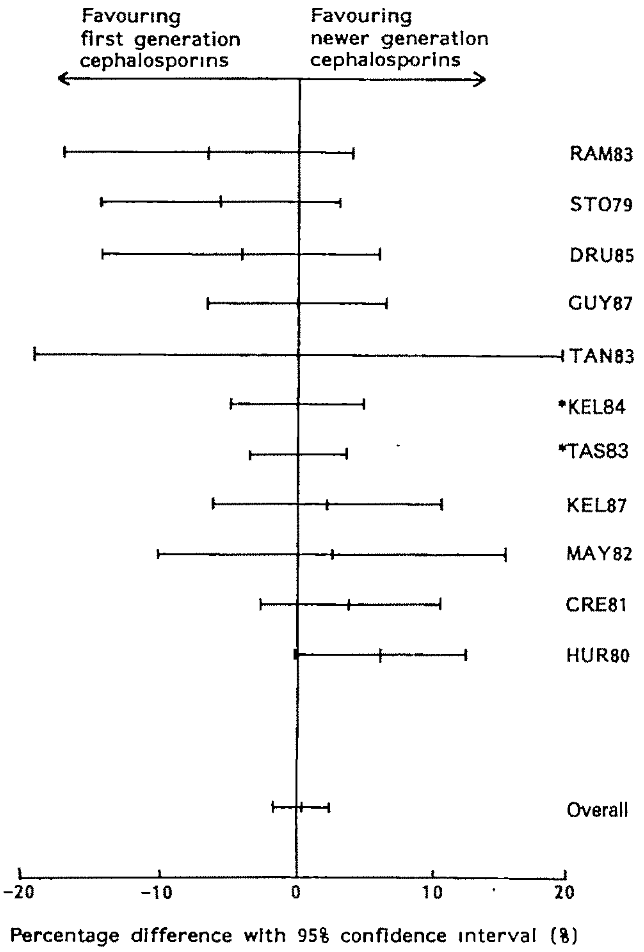

Figure 5 *Percentage differences with 95 per cent confidence intervals for 11 trials comparing first* versus *second or third generation cephalosporins and common 95 per cent confidence interval * Most informative trials, i e those with the smallest confidence intervals*

inspection; low risk, late inspection; high risk, early inspection; and high risk, late inspection) are 8, 10, 13 and 25 per cent respectively (all favouring treatment). The variation in definition of wound infection had no influence on treatment effect· there was no significant difference between major alone and major plus minor wound infections. Nevertheless, a better and widely accepted definition of wound infection is warranted to make comparison of different trials more reliable.

Results of the scoring system for study quality showed striking inadequacies in most analysed trials. These findings are quite comparable to a similar quality assessment of reports of antibacterial prophylaxis in colorectal surgery[28]. However, none of the different items of the scoring system had a significant influence on treatment effect

The meta-analyses of the trials from groups II and III showed that no greater benefit could be detected for the newer generation cephalosporins (in comparison with first generation the common percentage difference is 0·5 per cent) and for use of a multiple-dose regimen (in comparison with a single-dose regimen the common percentage difference is 0·4 per cent). From the confidence intervals it can be deduced that a difference larger than 2 per cent is unlikely Even if a 2 per cent difference were to be considered as interesting, a clinical trial to detect such a difference with statistical significance would need to include many thousands of patients. The small confidence intervals (3–4 per cent width) suggest that the choice of prophylactic agent can be made largely on the basis of cost.

An interesting question is whether meta-analysis can replace future clinical trials. The answer is no. Clinical trials in antimicrobial research should be carried out because one trial based on a single protocol, provided that sufficient patient numbers can be acquired, will always avoid the heterogeneity disadvantages inherent in an overview. One of the reasons for conducting such an analysis is to identify the need for and planning of major trials. Trials which have as primary objectives the comparison of single-dose *versus* multiple-dose regimens or first *versus* newer generation cephalosporins will almost certainly fail to detect any clinical or statistically significant differences with respect to the percentage wound infection rates. However, it has to be noted that almost all of the 15 group III trials (single *versus* multiple doseage) compared a multiple-dose, short-acting, first generation cephalosporin with a single-dose, long-acting, third generation cephalosporin. Therefore, we feel that a major trial comparing single *versus* multiple dosage of the same antimicrobial is still worthwhile

Although it is widely accepted that the first dose of prophylactic antibiotics should be given before operation, this was confirmed by only one prospective trial(Appendix A 36a). Recently, another randomized, double-blind trial[29] failed to show any advantage to starting antibiotics before operation. We endorse the view of Brumfitt and Hamilton-Miller[30], who made a plea for further studies into the timing of administration of prophylactic antibiotics.

In conclusion, antibiotic prophylaxis in biliary tract surgery is effective, especially in high risk patients. Late (follow-up) wound inspection essentially influenced the treatment effect

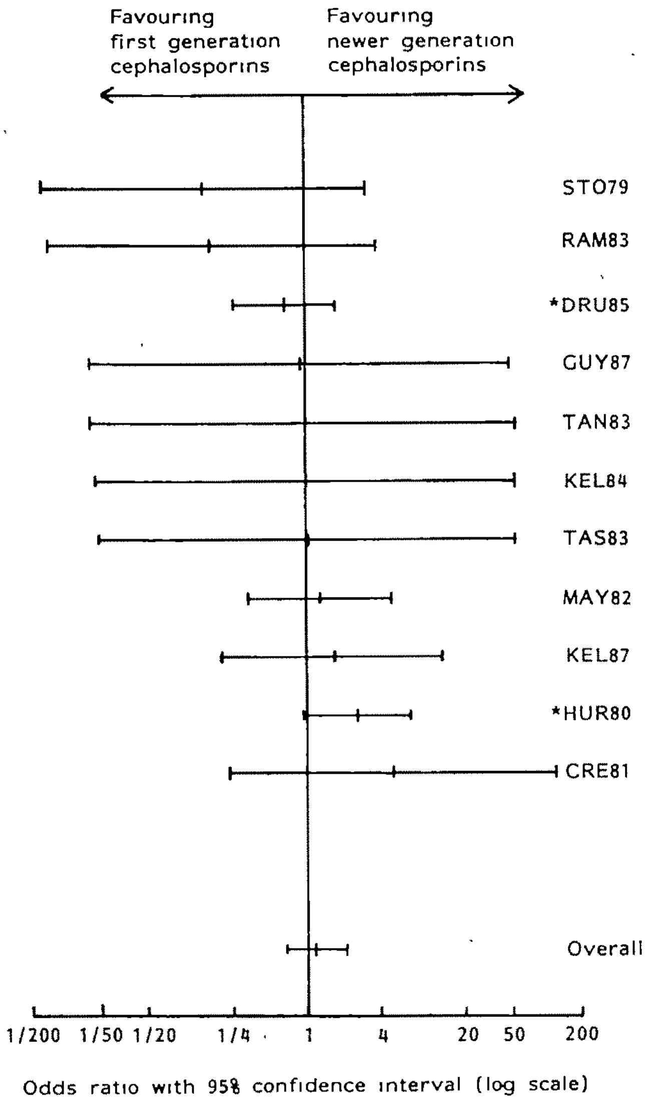

Figure 6 *Odds ratios with 95 per cent confidence intervals (log scale) for 11 trials comparing first* versus *second or third generation cephalosporins and common 95 per cent confidence interval * Most informative trials, i e those with the smallest confidence intervals*

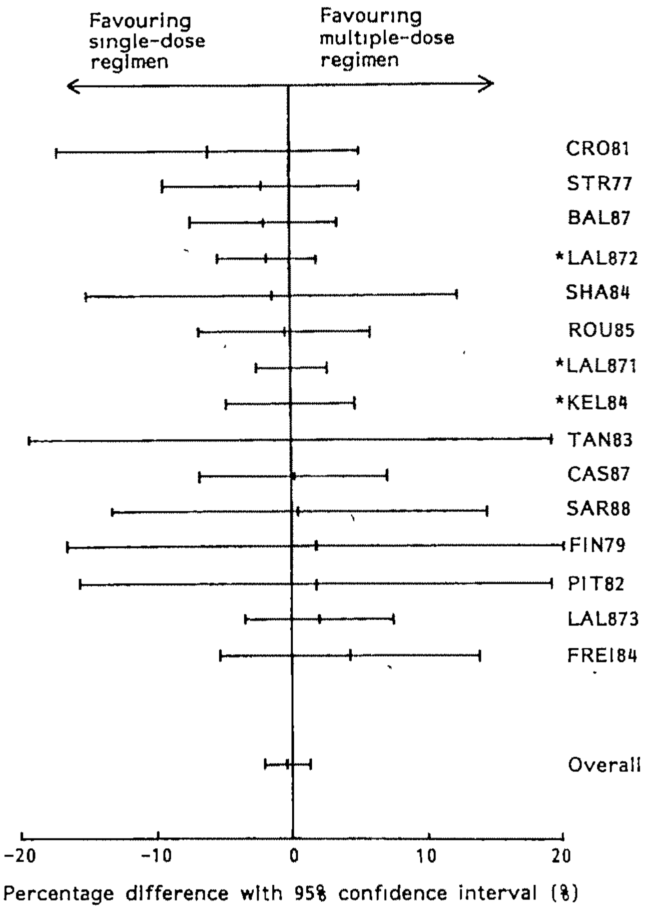

Figure 7 *Percentage differences with 95 per cent confidence intervals for 15 trials comparing single-dose* versus *multiple-dose regimens and common 95 per cent confidence interval. * Most informative trials, i.e those with the smallest confidence intervals*

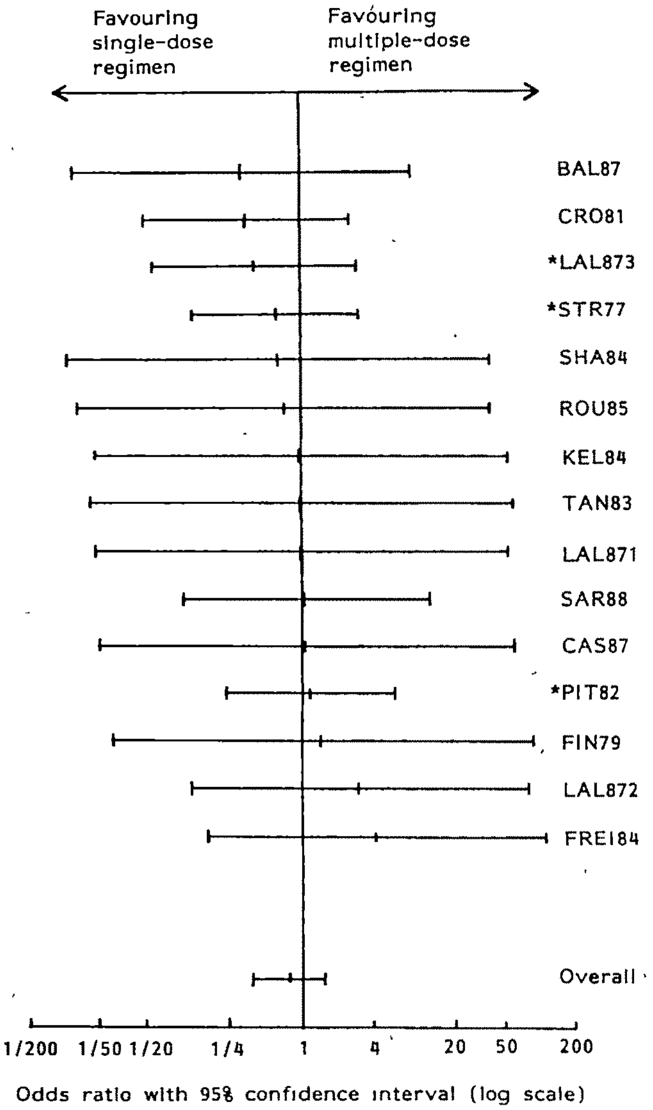

Figure 8 *Odds ratios with 95 per cent confidence intervals (log scale) for 15 trials comparing single-dose* versus *multiple-dose regimens and common 95 per cent confidence interval * Most informative trials, i.e those with the smallest confidence intervals*

reported. The choice of antimicrobial agent can largely be made on the basis of its cost. Future trials must be directed to the timing and duration of antibiotic prophylaxis, such as the need to give a first dose before operation and single *versus* multiple dosage of the same antimicrobial.

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Appendix A. Published trials accepted for meta-analysis

(*1*) *Studies used for comparison of treatment* versus *control* (*publication 21a contains two trials*)

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(In addition, publications 3a, 5a, 9a, 37a, 46a and 51a were used; publication 56a contains two trials.)

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Appendix B. Trials withdrawn from meta-analysis

(*1*) *Studies not eligible for one of the three groups of meta-analysis*

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15b Yellin AE, Berne TV, Heseltine PNR, Appleman MD, Gill MA, Leedom J. Sulbactam-ampicillin (SA) *versus* moxalactam as an adjunct to surgery for acute cholecystitis. *Proceedings of the 17th International Congress on Chemotherapy*, Istanbul, 1987. 1420–1 (Abstract).

(*2*) *Studies with sample size of less than ten*

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(*3*) *Studies with incomplete data* (*abstracts*)

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Operative findings in patients with early forms of gallbladder cancer

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Of 52 patients diagnosed as having gallbladder cancer in a 2-year period, 15 had no evidence of serosal involvement. Four of these 15 patients had tumour confined to the mucosa and did not undergo reoperation while 11 patients underwent lymph node dissection and hepatic wedge resection at a second operation. The correct diagnosis was suspected before the first operation in only one of 11 patients undergoing reoperation; the tumour was found microscopically in seven patients. Of the 11 patients who underwent reoperation, five had lymph node involvement, and three of these patients had both liver and lymphatic involvement. Our results underline the difficulty of establishing the diagnosis of gallbladder cancer before operation and the lack of major morbidity and mortality suggests that there may be value in reoperating on patients found to have gallbladder carcinoma without serosal involvement. Further follow-up is required to assess the long-term value of this approach.

Keywords: Gallbladder cancer, dissemination, reoperation, hepatic resection, lymphadenectomy

Gallbladder cancer is a relatively uncommon disease, although there is considerable geographical variation in its incidence. According to some reports the disease accounts for 3 per cent of all gastrointestinal tumours in countries such as the USA[1,2]. In Chile, gallbladder cancer is the second leading cause of death from tumours of the digestive system and the third cause of death from all malignancies[3]. Despite the improvement in diagnostic and surgical techniques, no change in survival rate has been observed[4–6]. This is mainly due to the late development of symptoms and direct extension of tumour to neighbouring organs at the time of diagnosis[7,8]. The use of aggressive surgery has not been associated with an increase in the survival rate of patients with advanced gallbladder cancer[4–6,9].

In order to improve the present level of diagnosis, ultrasonography has been employed to detect early forms of gallbladder cancer[10]. However, in the majority of patients with an early carcinoma, the diagnosis is normally made at operation or when studying the gallbladder specimen after cholecystectomy[11–15] The further treatment of patients in whom gallbladder cancer without serosal involvement is detected after cholecystectomy is still not well established. This is mainly because the reported series of patients are too small to reach definitive conclusions[9,11,12–16] With this in mind, we have reviewed our own experience of patients with gallbladder cancer without serosal involvement.

Patients and methods

In the period from January 1987 to December 1988, 1560 cholecystectomy specimens were studied at the Pathology Department of the Universidad de la Frontera. Immediately after cholecystectomy, specimens were fixed in formaldehyde and extended on paraffin blocks After 24 h of fixation, specimens were examined grossly and three haematoxylin and eosin stained sections were taken from the fundus and one from the body of each specimen. Multiple sections were taken from any area of the macroscopic abnormality.

In all, 52 gallbladder tumours were detected in the 1560 specimens Of these, 15 had no serosal involvement and are the subject of this study. All patients had undergone cholecystectomy as their first operation Four patients who had involvement limited to the mucosa were interviewed and were simply followed after operation Eleven patients with tumour involving the subserosa or muscular layers were interviewed and reoperation was advised. At reoperation a liver wedge resection was performed and lymph nodes of the first and second barriers were completely dissected (*Figure 1*) Furthermore, periaortic lymph node sampling was performed in four patients. Lymph nodes and gross appearance of tumours were classified as recommended by the Japanese Biliary Surgical Society (*Figure 1* and *Table 1*)

For statistical analysis, the χ^2 test was used and significance was assumed when $P<0{\cdot}05$.

Results

There were one male and 14 female patients, with ages ranging from 38 to 95 years and a mean of 59 years.

Table 2 shows details of the 11 patients in whom a second operation was performed. A correct diagnosis of cancer had been made before the initial operation in one of the patients, in whom a gallbladder mass was found on ultrasonography.

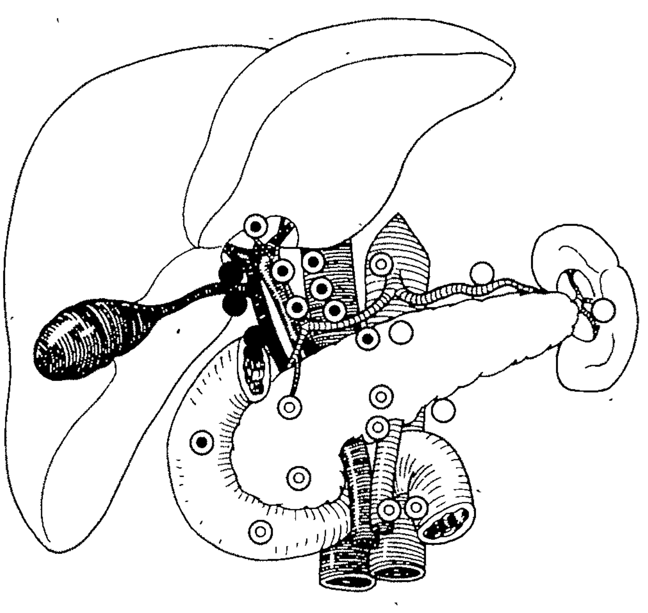

Figure 1 *Lymph node barriers according to the Japanese Biliary Surgical Society* ●, *First barrier,* ⊙, *second barrier,* ◎, *third barrier;* ○, fourth barrier

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An incorrect diagnosis of cholelithiasis alone was made in eight patients and of acute cholecystitis in six patients. Postoperative tumour diagnosis was made by macroscopic examination in four patients and by incidental microscopic examination in the remainder (*Table 3*).

With regard to the gross appearance (*Table 1*) of the tumours in the 15 patients diagnosed as having gallbladder cancer, one patient had type A, one had type B, three had type C, three had type D, four had type E and one patient had two different tumours (types C and D). One patient had an *in situ* tumour which seemed to be a combination of types A and E, and the final patient had an unclassifiable tumour.

With regard to the histological appearance of the tumours, a moderately differentiated adenocarcinoma was seen in nine patients; three patients had poorly differentiated tumours, and two had well differentiated tumours. One patient had an epidermoid type of tumour.

With regard to tumour dissemination, of the two patients in whom involvement was confined to the muscular layer, neither lymph node involvement nor hepatic infiltration was detected. In the nine patients with subserosal involvement, five had lymph node involvement and three of these five patients also had hepatic infiltration. Of the metastatic lymph nodes, those along the common bile duct were involved in two patients while lymph nodes located at the choledochoduodenal junction were involved in three patients. In one of the patients with choledochoduodenal lymph node involvement, metastasis to the lymph nodes around the hepatic artery was also observed. Furthermore, periaortic lymph nodes were involved in one of the four patients in whom they were recovered. In this patient, involvement of lymph nodes along the common bile duct was also detected

Delay from the first to the second operation ranged from 8 months to 20 days Elapsed time in the two patients with only lymph node involvement was 8 months and one of these patients had periaortic lymph node involvement. On the other hand, the elapsed time in the three patients with both liver infiltration and lymph node spread was 2, 2 and 1 month(s) respectively. In the patients without metastatic spread, elapsed time was less than 4 months, except for one patient with cancer involvement confined to the muscular layer who underwent reoperation 5 months after the first operation. In the 11 patients who underwent hepatic wedge resection and lymph node dissection, neither mortality nor major morbidity was observed. Minor complications were wound infection in one patient and transient gastric outlet obstruction in two patients. All patients were discharged 2 weeks after operation and are doing well, except for the patient who had periaortic compromise, in whom tumour recurrence has been detected 8 months after reoperation.

Discussion

Gallbladder cancer is a disease associated with a poor prognosis and a late diagnosis. Unfortunately symptoms are usually delayed until after the tumour has spread beyond the gallbladder wall[7], and cure is exceptional[6,9].

Nevin *et al.*[4] correlated the level of wall infiltration with prognosis; according to some reports the disease is potentially curable while tumour invasion is limited to the subserosal layers[11,12]. Of the potential pathways for dissemination, regional lymphatics, including the pericholedochal plexus and pancreatoduodenal lymph nodes, are the main routes of spread. Furthermore, gallbladder veins empty directly into the quadrate lobe of the liver[12,16]. Thus, treatment for gallbladder cancer should include lymph node dissection plus a wedge hepatic resection[11,12,16]. However, because of reports that show no benefit from aggressive therapy in patients with advanced

Table 1 *Gross appearance of gallbladder tumours according to the classification of the Japanese Biliary Surgical Society*

Type	Level of involvement	Description
A	Papillary	Tumours projecting into the lumen on a distinct pedicle
B	Nodular	Tumour without pedicle
C	Papillary infiltrative	Papillary tumours coexisting with infiltration
D	Nodular infiltrative	Nodular tumours coexisting with infiltration
E	Infiltrative	Diffuse infiltrative thickening of the wall

Table 3 *Pre- and postoperative diagnosis before histological examination and according to the level of wall invasion in 15 patients with gallbladder cancer but without serosal involvement*

	Preoperative		Postoperative	
Level of involvement	Cholecystitis or cholelithiasis	Tumour	Cholecystitis or cholelithiasis	Tumour
Mucosa	4	0	4	0
Muscular layers	2	0	1	1
Subserosa	8	1	6	3

Table 2 *Pathological findings in the 11 patients with gallbladder cancer who underwent reoperation*

Patient no.	Age (years)	Macroscopic type	Histology	Wall	Positive nodes	Liver infiltration
1	45	E	Moderately differentiated	Subserosal invasion	3/7	No
2	56	D	Well differentiated	Muscular invasion	0/13	No
3	65	C	Poorly differentiated	Subserosal invasion	0/9	No
4	50	C–D	Moderately differentiated	Subserosal invasion	3/8	No
5	69	A	Moderately differentiated	Muscular invasion	0/15	No
6	61	E	Moderately differentiated	Subserosal invasion	0/9	No
7	68	Unclassifiable tumour	Poorly differentiated	Subserosal invasion	1/10	Yes
8	48	E	Moderately differentiated	Subserosal invasion	2/12	Yes
9	38	C	Epidermoid	Subserosal invasion	1/5	Yes
10	44	D	Moderately differentiated	Subserosal invasion	0/19	No
11	54	C	Moderately differentiated	Subserosal invasion	0/17	No

tumours, we have restricted our treatment to patients without serosal involvement[12,16–18]. At the other extreme, because of the low possibility of metastatic spread in patients with mucosal tumours, we have not reoperated on these patients[4].

In our patients, the diagnosis of cancer was mainly achieved by studying the gallbladder specimen after cholecystectomy. In this context, ultrasonography has been advocated to detect early forms of gallbladder cancer, and promising results have been reported[10]. However, since the diagnosis was made only after microscopic analysis in some patients, ultrasonographic diagnosis may be very difficult. Because of this, we consider that, in countries with a high incidence of gallbladder cancer, prophylactic cholecystectomy in patients with gallstones should be borne in mind.

The number of patients with metastatic spread in our own series is too low to reach conclusions. However, in contrast with other reports which describe the liver as the most frequent site of spread[12], lymph nodes were the main route in our patients. Of the lymph nodes, those located at the choledochoduodenal junction and along the common bile duct were most often involved. The presence of metastatic involvement at the choledochoduodenal junction is important since this is the last step before involvement of the retropancreatic nodes. To extirpate the retropancreatic nodes completely, pancreaticoduodenectomy would be necessary, thus adding further morbidity and risk of mortality to the treatment of gallbladder cancer.

The relationship between the histological type of tumour and prognosis has been described previously[12,17,18]. In our patients, the low number with metastatic lymph nodes prevents comparison of these variables.

The elapsed time between cholecystectomy and reoperation may have an influence on the operative findings, thus explaining the presence of periaortic lymph node involvement in one of our patients who underwent reoperation after 8 months. In this patient, cancer was diagnosed before implementation of the treatment protocol and this was the reason for delay. In future, to study the difference in clinical behaviour associated with different tumours, we intend to take into account variables such as DNA ploidy pattern, which we have already shown to be linked to prognosis in patients with early gastric cancer[19,20].

Finally, with regard to treatment, in all except one of our patients, curative resection was performed and neither death nor major morbidity was observed. Lymph node dissection around the hepatic artery may explain the gastric outlet obstruction noted in two patients on the basis of denervation of the pyloric area. From our results, we can say that despite the low curative resection rate of gallbladder cancer, when cancer is diagnosed at an early stage, curative resection can be undertaken safely. Furthermore, because of the incidence of lymphatic and liver involvement among patients without serosal involvement, we advocate reoperation in patients in whom the diagnosis is made by studying the gallbladder specimen. Further follow-up is needed to assess the long-term value of reoperation in these patients.

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The effect of caerulein induced pancreatitis on the hepatic microvasculature

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A three-dimensional morphological study of the hepatic microvasculature in caerulein induced oedematous pancreatitis was performed using scanning electron microscopy (SEM) vascular casts and transmission electron microscopy (TEM) of hepatocytes and hepatic sinusoids. TEM studies provided ultrastructural evidence of hepatocellular damage while SEM views demonstrated gross irregularity of the sinusoidal outline with abruptly terminating sinusoidal buds and extravasation of cast material, findings which were similar to those previously reported in the pancreas itself using the same model and which were supported by TEM cross-sectional views of the hepatic sinusoids. The results suggest that caerulein induced pancreatitis is associated with extrapancreatic microvascular damage which may be an important factor in the pathogenesis of extrapancreatic organ impairment associated with acute pancreatitis.

Keywords: Pancreatitis, liver, microvasculature

Acute pancreatitis may be associated with hepatic dysfunction[1,2], but this association is rarely highlighted and poorly understood[3]. Indirect perfusion studies of the isolated *ex vivo* pancreas suggest that pancreatitis may be associated with increased capillary permeability[4] and recent electron microscopic studies of vascular casts of the pancreas have demonstrated gross distortion of the local microvasculature in caerulein induced pancreatitis[5]. Using a similar corrosion casting technique this study evaluated the effect of caerulein induced pancreatitis on the hepatic microvasculature and hepatocellular ultrastructure.

Materials and methods

Ten Sprague-Dawley rats (mean weight 520 g, range 410–600 g) were anaesthetized using an intraperitoneal injection of chloral hydrate. Five animals (group 1) received a 4 h intravenous infusion of caerulein ($5\ \mu g\ kg^{-1}\ h^{-1}$) diluted in a 1:10 saline dilution of rat serum and infused at a rate of $0{\cdot}25\ ml\ h^{-1}$. Caerulein, an analogue of cholecystokinin, is a stimulant of pancreatic exocrine secretion but when administered to rats in supramaximal doses ($5\ \mu g\ kg^{-1}\ h^{-1}$) induces an oedematous interstitial pancreatitis[6]. Five rats (group 2) received a similar volume of a 1:10 saline dilution of rat serum alone. Blood was taken for serum amylase estimation prior to infusion and again at the end of the infusion period. Laparotomy was then performed, the inferior vena cava was cannulated above the level of the hepatic veins with a 16 Fr cannula and the liver was perfused retrogradely with saline (10 ml) and then with glutaraldehyde (10 ml). The organ was perfused 20 min later with Mercox® (Ladd Industries, Vermont, USA) (10 ml), a low resistance casting medium, which was allowed to dry and harden over a further 20 min.

The cast organ was then digested in 30 per cent potassium hydroxide at 36°C, washed to neutrality with water, dried in air, coated with gold and examined by scanning electron microscopy (SEM). Biopsies of liver perfused with saline and glutaraldehyde alone were prepared for transmission electron microscopy (TEM). Sections were stained with uranyl acetate and lead nitrate and the hepatocellular ultrastructure and hepatic microvasculature were examined in a JEOL 35C electron microscope (JEOL UK Ltd, London, UK)[7].

Results

Group 1 animals all developed pancreatitis as evidenced by a significant rise in serum amylase levels at the end of the 4 h infusion period (mean(s.e.m.) serum amylase level prior to infusion 5600(365) units/l; mean serum amylase level at 4 h 27 580(1420) units/l), gross appearances at laparotomy and the typical histological changes in intracellular oedema, reduction in the number of zymogen granules and an increase in the number of cytoplasmic vacuoles within the acinar cells, all of which have been described previously[3]. TEM of the hepatocytes revealed evidence of ultrastructural damage with the appearance of intracellular vacuoles and loss of outline of the cristae of the hepatocellular mitochondria (*Figure 1*). SEM of casts of the hepatic sinusoids in animals with pancreatitis demonstrated gross irregularity in outline, abruptly terminating vessels and extravasation of cast materials (*Figure 2*). These findings were supported by cross-sectional TEM of the hepatic sinusoids (*Figure 3*).

Discussion

Acute pancreatitis may be complicated by extrapancreatic organ impairment[8] notably renal[9,10] and respiratory[11,12]. It may also be associated with hepatic dysfunction[1,2], a complication that is not confined to those cases of pancreatitis induced by gallstones. The recent demonstration of distortion of the local microvasculature in an experimental oedematous pancreatitis model[5] raises the possibility that similar distortion may occur in other organs. This study confirms that caerulein induced pancreatitis is associated with both hepatocellular and hepatic microvascular damage.

The caerulein model is simple, non-invasive, highly reproducible, and slow to evolve[6,13]. Although its clinical relevance is still unclear, the morphological changes are consistent with those of human acute pancreatitis and it is generally accepted as a suitable model for studies of different therapies[13]. If further work confirms that experimental pancreatitis is associated with a diffuse microvascular injury then specific treatments preventing destabilization of cell membranes, both endothelial and epithelial[1,14,15], should be further evaluated.

The microvasculature of the normal rat liver, as displayed in control animals in this study is similar to that previously described in rodents by Kardon and Kessel in 1980[16] with a dense interlacing network of smoothly outlined hepatic sinusoids fed directly by terminal branches of both the portal venous and the hepatic arterial system. They also described abruptly ending sinusoids near the surface of the liver but those vessels were smooth in outline and represented the termination

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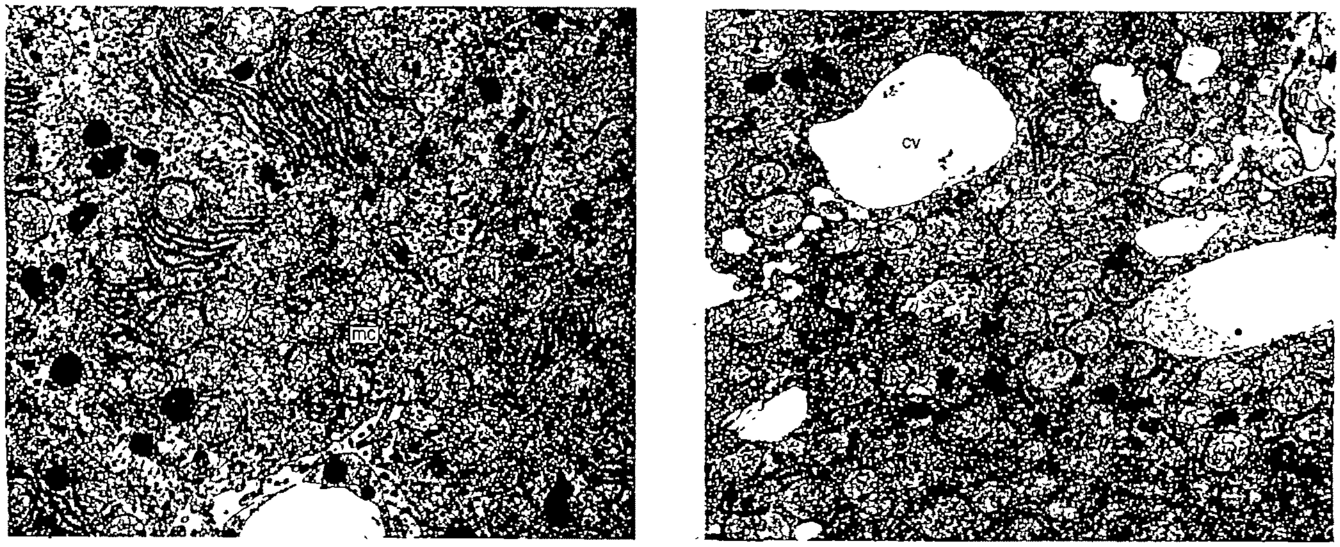

Figure 1 *Transmission electron microscopic views of hepatocytes after* **a** *saline and* **b** *caerulein infusion showing loss of outline of mitochondrial cristae (mc) and increase in cytoplasmic vacuoles (cv)* (×*10 000*)

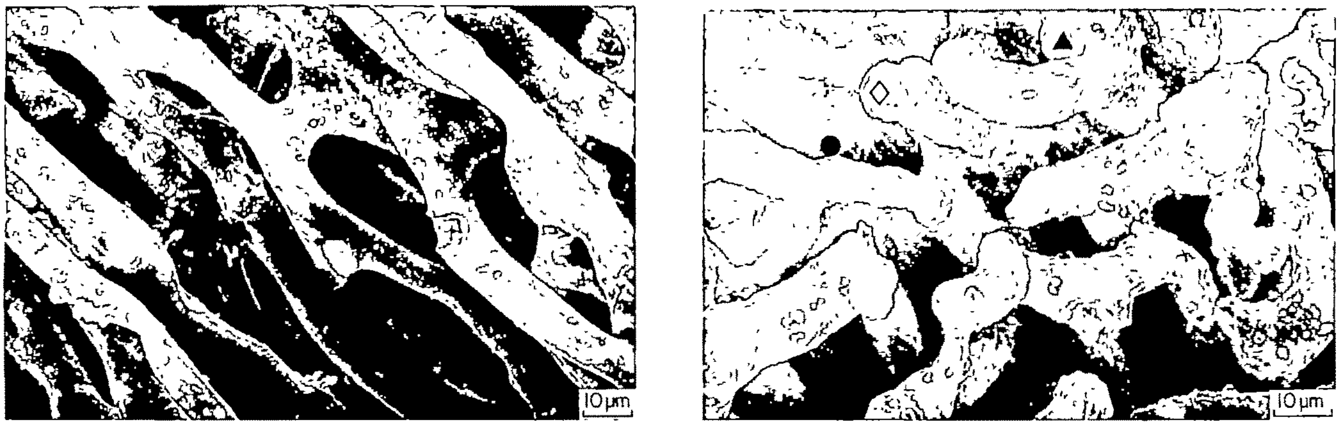

Figure 2 *Scanning electron microscopic views of casts of hepatic sinusoids after* **a** *saline and* **b** *caerulein infusion showing gross irregularity in sinusoidal outline,* ●, *abruptly terminating vessels,* ◇, *and extravasation of cast material,* ▲ (×*2000*)

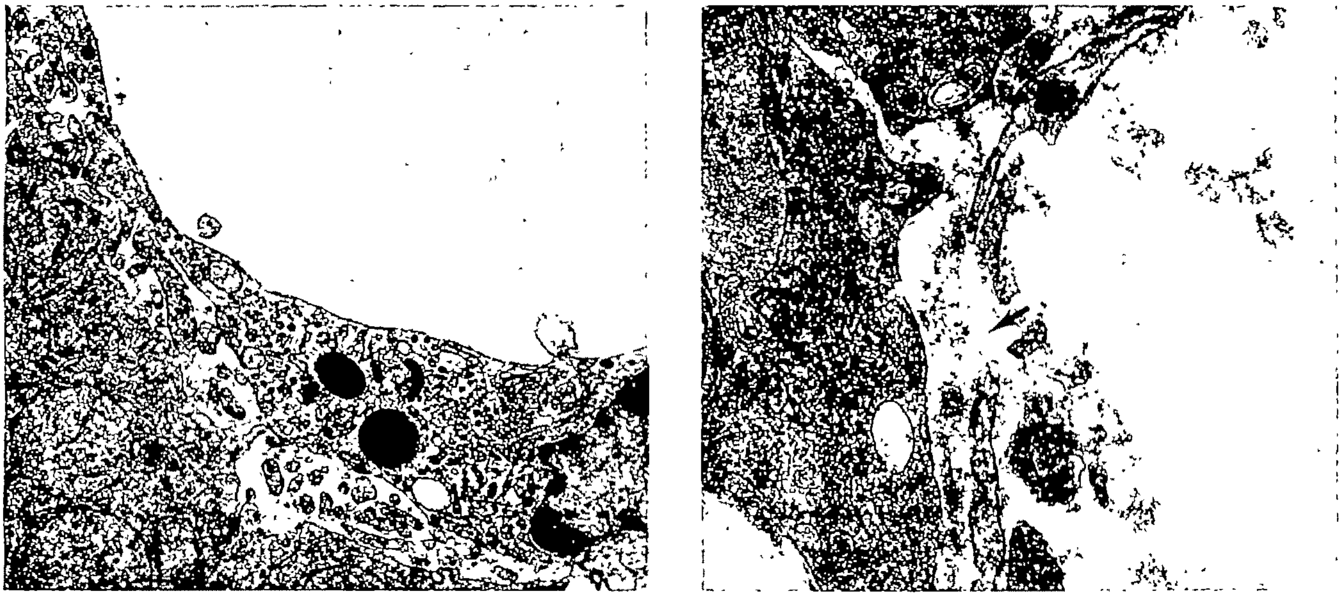

Figure 3 *Transmission electron microscopic views of hepatic sinusoids after* **a** *saline and* **b** *caerulein infusion showing disruption of the sinusoidal lining (arrow)* (×*67 000*)

of the sinusoids at the periphery of the radial type of the hepatic lobule[16]. The short abruptly terminating irregular sinusoidal buds seen within the hepatic lobules of the animals with pancreatitis in this study are clearly different from the above and were not seen in the control animals. The cause is unclear but similar appearances were seen in the pancreas in the same model[5]. No evidence of capillary thrombosis was seen either on light microscopic or TEM views of pancreatic capillaries or hepatic sinusoids.

The ultrastructural changes seen in the hepatocytes in this study have also been reported in association with other models of pancreatitis[1,2] and are similar to many of the non-specific changes seen in the acinar cell of the pancreas itself[6]. These changes represent significant cell damage but are not specific for pancreatitis[13] The simultaneous development of similar changes in both the liver and pancreas, however, in caerulein induced pancreatitis suggests a common underlying cause.

Distortion of the hepatic microvasculature in association with pancreatitis has not been reported previously but the pattern of distortion is very similar to that reported in the pancreas itself[5]. The irregularity of the cast surface and leakage of the cast medium on SEM supported by the TEM findings suggests disruption of the sinusoidal lining with altered permeability: a factor recently implicated in the pathogenesis of pancreatitis[4]. The hepatic disruption may be due to a direct effect of caerulein, but the proximity of the liver to the pancreatic venous effluent suggests a possible role for vasoactive metabolites released from the inflamed pancreas[17]. Work is currently in progress to study the direct effect of caerulein on the microvasculature of the liver and other organs known to be impaired in acute pancreatitis.

This study demonstrates that even in mild oedematous pancreatitis such as that induced by caerulein, distortion of extrapancreatic microvasculature occurs. This distortion may be a critical factor in the development of extrapancreatic organ impairment which occurs in association with acute pancreatitis, particularly of the haemorrhagic variety.

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Management of gastric variceal haemorrhage

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From March 1979 to April 1988 nine patients with hepatic cirrhosis have presented with acute variceal haemorrhage from gastric varices. Of six patients who underwent emergency laparotomy those with modified Child's grade C (n = 3) *died within 30 days of surgery. Six patients have been followed for 2 years or longer. In the three patients who underwent under-running of gastric varices alone, two patients developed oeosophageal varices at 3 and 14 months, respectively, and in the third patient gastric varices recurred 3 years after surgery. In the remaining three patients, additional left gastric vein ligation was not associated with recurrence of gastric varices or the development of oesophageal varices.*

Keywords: Hepatic cirrhosis, portal hypertension, oesophagogastric varices, haemorrhage, injection sclerotherapy

Clinically significant gastric varices are uncommon[1] and may be classified into four varieties: (1) those associated with oesophageal varices; (2) those developing or remaining after obliteration of oesophageal varices; (3) those associated with splenic vein obstruction; and (4) isolated gastric varices. It is well recognized that the commonest cause of oesophagogastric varices is portal hypertension, secondary to hepatic cirrhosis, but primary haemorrhage from gastric varices in such patients is uncommon with an incidence of 3·5 per cent in the 230 patients studied by Watanabe and colleagues[2]. Several large studies of patients with oesophagogastric varices do not mention the management of isolated gastric varices[3–6]. Such varices are commonly associated with splenic vein obstruction which in turn is usually secondary to pancreatic disease[7,8].

Our experience of nine patients with gastric variceal haemorrhage is reviewed.

Patients and methods

Between March 1979 and April 1988 nine patients presented to the University Department of Surgery, Royal Infirmary, Glasgow with endoscopically or surgically proven gastric variceal haemorrhage, representing 3·8 per cent of the 235 patients with oesophagogastric varices admitted to the unit during that period. These patients were evenly distributed throughout the 9-year period. A summary of the clinical data is shown in *Table 1* There were five women and four men with a mean age at presentation of 57 years (range 44–74 years) and all had underlying biopsy-proven hepatic cirrhosis (alcoholic cirrhosis in six, cryptogenic in two, and primary biliary in the remaining patient, numbered patients 1–9).

Patients 1–6 had isolated gastric varices with no evidence of preceding or concomitant oesophageal varices Patients 7–9 all had endoscopically documented evidence of previous oesophageal varices, and two patients had undergone injection sclerotherapy with obliteration of the oesophageal varices

Diagnosis of gastric varices

The diagnosis of gastric varices was made in six patients (Nos 3, 5–9) before operation at endoscopy Patient 6 had been admitted to another hospital on two previous occasions with upper gastrointestinal haemorrhage which was thought to have arisen from gastric erosions and 28 units of blood had been transfused. On admission to our unit, the diagnosis of bleeding gastric varices was made at endoscopy In patients 2 and 4 active bleeding at the time of endoscopy obscured the lesion, which was presumed to be a gastric ulcer within the fundus In patient 1 the gastric varices were mistakenly diagnosed as a haemangioma at endoscopy.

Results

Of the nine patients, three (Nos 1, 3 and 9) underwent elective treatment of gastric varices which had previously been shown to be the source of major blood loss In two of these patients (Nos 3 and 9) the diagnosis had been made before operation. Both of these patients underwent attempts to outline the splenic vein, by digital subtraction angiography in one and coeliac angiography in the other, but these investigations failed to outline the portal venous system satisfactorily. In the third patient (No. 1) splenoportography 2 months after operation revealed a patent splenic vein and a raised portal pressure of 33 mmHg. In the remaining six patients (Nos 2, 4–8) emergency surgery was undertaken because of continuing haemorrhage. Of the three patients surviving the procedure, one (No. 4) underwent splenoportography following surgery which demonstrated a patent splenic vein and an increased portal pressure of 27 mmHg. In one further patient (No. 8), a decision was made not to carry out splénoportography after operation because of the presence of metastatic breast carcinoma. The final patient (no. 2) refused further investigation.

Patient No. 5 presented first to another hospital and was treated after endoscopy by the insertion of a 4 lumen Minnesota tube. Endoscopy had shown a large clot adherent to the lower oesophagus and upper stomach. Five days later she was transferred to the Royal Infirmary in a comatose condition with deteriorating respiratory function. The Minnesota tube was removed and upper gastrointestinal endoscopy was repeated. This showed an oesophagopleural fistula, the oesophageal defect extending from 28 to 34 cm. This defect may have been caused by prolonged inflation of the oesophageal balloon, possibly at the wrong pressure. There was no evidence of oesophageal varices, but within the fundus there was a large gastric varix with adherent clot. She underwent emergency subtotal oesophagectomy with cervical oesophagostomy, under-running of the gastric varix and insertion of a tube gastrostomy and feeding jejunostomy. The patient died 5 days later from combined cardiac, renal and hepatic failure.

Of the remaining eight patients, three underwent elective operation once bleeding had ceased, and five had emergency surgery because of continuing haemorrhage. All patients had the gastric varices under-run following anterior gastrotomy. Four patients also had ligation of the left gastric vein with division of the short gastric vessels in one and a splenectomy in another Three patients with modified Child's grade C died following emergency surgery. Patient 5 has already been mentioned. Patient 6 died of progressive liver failure 22 days after surgery without experiencing further upper gastrointestinal haemorrhage. Patient 7 had a severe coagulopathy and continued to bleed after his emergency laparotomy. At relaparotomy no specific bleeding site could be identified and the patient died 24 h later.

The remaining six patients have been followed for an average

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Table 1 *Clinical data on nine patients with gastric variceal haemorrhage*

Patient No.	Sex	Age (years)	Child's grade	Surgery	Follow-up
1	F	66	B	Elective Under-run	Developed oesophageal varices after 14 months (injected) No gastric varix recurrence 5 years
2	M	47	A	Emergency. Under-run	Developed oesophageal varices after 3 months (injected) No gastric varix recurrence 6 years
3	F	66	A	Elective. Under-run + LGV ligation	No oesophageal or gastric varices 2 years
4	F	46	B	Emergency. Under-run + LGV ligation + division of SGV	No oesophageal or gastric varices 3 years
5	F	60	C	Emergency. Under-run + subtotal oesophagectomy	Died 5 days
6	M	50	C	Emergency Under-run + LGV ligation	Died 22 days
7	M	62	C	Emergency. Under-run	Died 24 days
8	F	74	B	Emergency. Under-run	Recurrence of gastric varices at 3 years (injected). Died 2 years later (metastatic breast carcinoma)
9	M	44	B	Elective. Under-run + LGV ligation + splenectomy	No oesophageal or gastric varices 2 years

LGV, left gastric vein; SGV, short gastric vessels

of 4 years (range 2–6 years). One patient has developed a small recurrent gastric varix 3 years after surgery. This varix was injected and the patient remained free of haemorrhage until her death 2 years later from metastatic breast carcinoma. Two patients have developed oesophageal varices detected at endoscopic review at 3 months and at 14 months. The oesophageal varices have been obliterated using injection sclerotherapy. Three patients have remained free of both oesophageal and gastric varices after 2, 2 and 3 years of endoscopic follow-up.

Discussion

Our experience confirms that clinically significant gastric varices may be difficult to diagnose. This may result from a lack of awareness of the condition as a separate entity or because of the relative inaccessibility of the posterior wall of the gastric fundus to endoscopy, especially in the presence of haemorrhage Three of our patients (Nos 1, 2 and 4) with isolated gastric varices had the true source of bleeding identified at laparotomy, haemorrhage from the varices having obscured the lesion at endoscopy in two patients. None the less, the mainstay of diagnosis remains upper gastrointestinal endoscopy, although it may be difficult on occasions to distinguish gastric varices from normal mucosal folds, gastritis or vascular ectatic lesions[9–11]. This may account for the wide variation (0–33 per cent) in the incidence of gastric varices reported by others[12–14].

The radiological demonstration of fundal varices by conventional contrast studies is notoriously difficult[15–17], although double contrast examination is said to allow visualization of these varices in 80 per cent of patients[14,18]. The diagnosis may be confirmed by angiography or transplenic portovenography[15,16,19], but caution is required in interpreting the radiographs as retrogastric collaterals can easily be mistaken for gastric varices. In the emergency situation it is rarely possible to carry out these investigations and these invasive investigations may be contraindicated when a coagulation defect exists[20]. In the present study four patients underwent investigation to outline the splenic vein but this was only successful in the two patients who had direct splenoportography which delineated a patent splenic vein and detected elevated portal pressures.

Isolated gastric varices in the absence of oesophageal varices can be explained satisfactorily if splenic vein obstruction has occurred. In this left-sided[21] or segmental[22] portal hypertension there is reversal of blood flow between the fundus of the stomach and the spleen; splenic blood passes directly through the short gastric veins to the fundus where varices are formed[23]. In patients with a patent splenic vein, it is difficult to account for the presence of isolated gastric varices. In 209 cases of splenic vein obstruction causing segmental hypertension reported in the English literature between 1900 and 1984, only nine (4·3 per cent) patients had associated cirrhosis which in all cases was accompanied by signs of generalized and segmental portal hypertension[8,24].

Previous injection sclerotherapy in patients 7 and 9 had obliterated the oesophageal varices and may have resulted in an increased flow of portal blood across the fundus of the stomach, promoting the development of gastric varices. If this was the only factor involved, more patients would be expected to demonstrate gastric varices after obliteration of their oesophageal varices.

The most appropriate method of treatment for gastric variceal haemorrhage is controversial. The efficacy of balloon tamponade in the initial control of bleeding oesophagogastric varices is well established[25]. When the haemorrhage originates from gastric rather than oesophageal varices, the Linton-Nachlas tube has been used in preference to the Minnesota tube to control variceal bleeding[26,27]. Previous reports (excluding those dealing with splenic vein obstruction) have dealt with fewer than four cases and most have limited follow-up[17,28–33]. In these patients, surgical treatment has included ligation of the varices and two-thirds gastrectomy[29], oesophagogastrectomy and splenectomy[30], splenectomy alone[30], proximal gastrectomy[31], and selective variceal decompression by shunting blood between the splenic vein and the left gastric vein, left gastroepiploic vein or the interior mesenteric vein[28].

Splenic vein patency is a useful determinant of definitive treatment. When isolated gastric varices are due to splenic vein obstruction, splenectomy cures almost 90 per cent of patients with a low incidence of recurrent bleeding[8,24]. When the splenic vein is patent, splenectomy is inappropriate unless required to provide access to allow a devascularization procedure. The options are to under-run the gastric varices, with the addition of left gastric pedicle ligation, division of the short gastric vessels and/or ligation of the perioesophageal veins. More than one of these procedures may be appropriate in different individuals.

Although the condition is uncommon, the clinician should be aware of its existence since a delay in diagnosis may be detrimental to the patient. From our limited experience, bleeding gastric varices are best controlled by under-running, and recurrence of the gastric varices or the development of oesophageal varices are prevented by some form of devascularization procedure. Splenectomy should be reserved for those patients whose gastric varices are secondary to splenic vein obstruction.

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Case report

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Non-preservation of the pylorus in resection of pancreatic cancer

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In 1978 preservation of the pylorus during pancreaticoduodenectomy was advocated to prevent the undesirable gastrointestinal side effects of partial gastrectomy[1,2]. This modification of the standard Whipple partial pancreaticoduodenectomy or total pancreaticoduodenectomy was originally intended for patients with chronic pancreatitis or distal duodenal cancer. Soon the indications were broadened to include periampullary and pancreatic cancers. Data available so far suggest no difference in operative mortality and survival duration between the standard pancreaticoduodenectomies and the pylorus-preserving variant when used to treat cancer[3–5]. However we have encountered two successive patients with cancer of the pancreatic head who both had a tumour-positive duodenal resection margin after a pylorus-preserving pancreaticoduodenectomy that was otherwise oncologically radical.

Case histories

A 63-year-old man, otherwise in good general health, was admitted with painless, obstructive jaundice caused by a tumour in the head of the pancreas. At operation a 4 cm tumour was found anteriorly in the uncinate process and head of pancreas, close to the body of the pancreas and adherent to the base of the superior mesenteric vein. No tumour dissemination could be found Frozen section investigation of the retropancreatic and hepatoduodenal lymph nodes was negative

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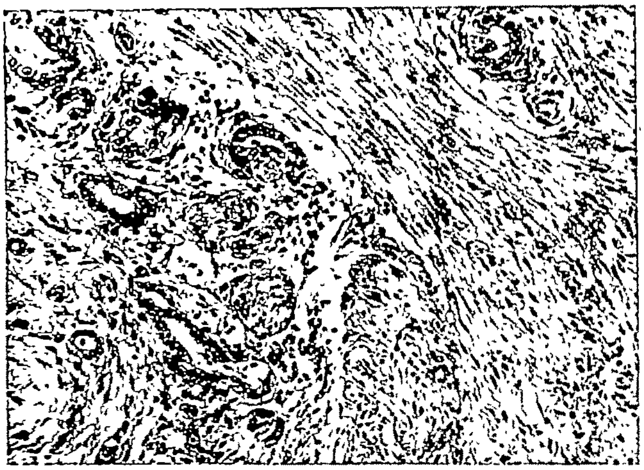

Figure 1 *Adenocarcinoma infiltrating in tunica muscularis of the duodenal wall at the resection margin (haematoxylin and eosin, original magnification ×125)*

Total pancreaticoduodenectomy was carried out including resection of the superior mesenteric vein and its two main tributaries. As the proximal duodenum appeared macroscopically free of tumour, the stomach and pylorus were preserved and the duodenum was transected 2 cm beyond the pylorus. The mesenteric vein was replaced by the preserved, transposed splenic vein and duodenojejunal and hepaticojejunal continuity was restored in the usual way

Postoperative abdominal recovery was uneventful until serious respiratory problems followed aspiration and the patient then developed cerebral infarction, resulting in hemiparesis and total visual agnosia. Histological examination revealed a 4 cm adenocarcinoma without lymphatic dissemination. The resection margins were free of tumour except in the transected duodenal wall (*Figure 1*). Given his neurological condition, reoperation was not undertaken. Six months later the patient was otherwise in good health.

The second patient, a 66-year-old lady, was operated upon for cytologically proven adenocarcinoma in the head of the pancreas causing obstructive jaundice. This operation took place 5 days after the operation on the first patient and just before his histological report was known. At operation a 3 cm tumour was found in the head of the pancreas close to the duodenum. No metastases could be found. Frozen section examination of retroduodenal and hepatoduodenal lymph nodes revealed no tumour. The proximal duodenum appeared free of tumour and a pylorus-preserving partial pancreaticoduodenectomy was carried out with transection of the duodenum 1·5 cm from the pylorus. The pancreatic and biliary resection margins were tumour-free at frozen section examination. Peroperative examination of the duodenal resection margin was not performed.

Postoperative histological examination revealed a pancreatic adenocarcinoma infiltrating the muscle layer of the duodenum. There was one micrometastasis in a lymph node between the pancreas and duodenum. The other lymph nodes were free of tumour All resection margins were free of tumour except for the resection margin through the proximal duodenum

The general postoperative recovery of the patient was good but gastric emptying was impaired. Two weeks later a 50 per cent distal gastrectomy was performed with excision of the duodenojejunostomy and Roux-en-Y reconstruction. Gastrojejunal function slowly recovered and the postoperative course was otherwise uneventful No tumour rests were found in the resected duodenojejunostomy and duodenal cuff. Six months later the patient is in good health.

Discussion

Except for the tumour-positive duodenal margin, surgical radicality was achieved at all other resection margins in both patients. These two case histories illustrate the possibility of leaving an avoidable positive resection margin in the proximal duodenum as a result of the pylorus-preserving resection for pancreatic cancer. Standard partial gastrectomy would have avoided this problem.

An intact neurovascular supply to the pylorus and first part of the duodenum is essential for the success of pylorus-preserving pancreaticoduodenectomy. Therefore the right gastric artery is preserved and the right gastroepiploic artery is cut at its origin from the anterior pancreaticoduodenal artery on the head of the pancreas[6]. Preservation of the vagal supply of the pylorus requires dissection at a distance from the pylorus and the duodenal wall. Consequently the dissection closely follows the cranial and anterior surface of the pancreatic head, and the subpyloric and superior pancreatic head nodes with adjacent surrounding soft tissues, which might be involved by tumour[7,8], are left undisturbed. The possibility of the tumour extending along the duodenal wall is also not dealt with in pylorus-preserving pancreaticoduodenectomy. Our case histories show that a duodenal cuff macroscopically free of tumour is no guarantee of microscopic radicality. Peroperative frozen section examination is imperative.

Partial gastrectomy as part of a pancreaticoduodenectomy for pancreatic cancer should not be omitted in favour of the dubious advantage of pylorus preservation. Early postoperative disadvantage of the pylorus-preserving pancreaticoduodenectomy consisting of deficient gastric and pyloric function is well documented[3,9,10] and recently the long-term advantages have also been questioned[11]. Marginal ulceration can be avoided by performing a large gastric resection[12] and gastrointestinal reflux can be avoided by construction of a Roux-en-Y gastrojejunostomy. It is not justified to jeopardize the only chance of cure the patient has by omitting partial gastrectomy during pancreaticoduodenectomy for pancreatic cancer.

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Towards decreasing the relaparotomy rate in the Peutz–Jeghers syndrome: the role of peroperative small bowel endoscopy

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Relaparotomy occurs commonly in patients with the Peutz–Jeghers syndrome, and at quite short intervals. Between 1943 and 1987 laparotomies were performed on 54 occasions in 23 patients with the Peutz–Jeghers syndrome who at some time came under the care of St. Mark's Hospital. In four patients repeat laparotomy was performed within a single year. Between 1987 and 1989 a further five patients have undergone laparotomy with on-table small bowel endoscopy. External palpation and small bowel transillumination failed to demonstrate 17 out of a total of 45 hamartomas (38 per cent). Of these 17 polyps identified endoscopically, 11 (65 per cent) were sufficiently large that a snare was used to remove them. We recommend peroperative enteroscopy as an adjunct to surgery in the Peutz–Jeghers syndrome.

Keywords: Peutz–Jeghers syndrome, endoscopy

The autosomal dominant syndrome of mucocutaneous pigmentation and diffuse gastrointestinal polyposis was first described by Peutz in 1921[1] and Jeghers *et al.* in 1949[2]. A 'laissez-faire' approach to the management of what are mostly, but not always[3], benign gastrointestinal hamartomas has led to surgery being performed mainly for complications caused by these polyps, with a consequent high recurrent laparotomy rate and related morbidity and mortality[4]. In the first part of this paper we present data on 23 patients with the Peutz–Jeghers syndrome to establish their rate of relaparotomy. In the second part we have evaluated the effect of introducing peroperative enteroscopy on the number of polyps found and removed.

Patients and methods

Patient survey

Between 1943 and 1987 23 patients with Peutz–Jeghers syndrome were seen in outpatients at St. Mark's Hospital. A questionnaire was sent to the 20 surviving patients asking at what age laparotomies were performed and how frequently they were done Hospital records were used to obtain information on the three deceased patients and on the indications for surgery in all patients

Peroperative enteroscopy study

In 1987 we started a prospective study of peroperative small bowel endoscopy from the duodenum to the ileocaecal valve using a flexible endoscope. All patients received intravenous metronidazole and gentamicin at induction of anaesthesia. A paediatric colonoscope (Olympus PCF10, Keymed Ltd , Southend-on-Sea, UK) was passed through the mouth and guided along the small bowel by the abdominal operator or an adult gastroscope (Olympus GIFXQ10· Keymed Ltd.) was introduced through an enterotomy Before oral insertion of the paediatric colonoscope, endoscope disinfection was achieved by washing the instrument in a 2 per cent glutaraldehyde solution (Cidex®, Surgikos Ltd , Livingston, UK) for 12 min using an Olympus EW-20 washing machine (Keymed Ltd.) followed by all-channel irrigation and wiping of the handle and connecting tube with 70 per cent alcohol and of the outer tube with 30 per cent alcohol. Before direct insertion of the gastroscope through an enterotomy, three additional precautions were taken; the instrument was soaked in Cidex® for 12 h, the immediate operative field was protected with packs, and gloves were changed as for a dirty procedure. Endoscopy was performed after the abdomen had been opened and after the number of polyps had been determined by transillumination and palpation.

Results

Patient survey

All 20 patients responded to the questionnaire. Operations started at a young age and were frequently repeated, often over a short space of time (*Table 1*). Of the 31 relaparotomies, polyp-induced complications were responsible for 23 (74 per cent), adhesions for two (6 per cent) and the reason was unknown in six cases (19 per cent) because many of the

Table 1 *Laparotomy record*

Patient No.	Sex	Age at laparotomies (years)	Years since last laparotomy
1	F	29	46
2	M	11, 11, 21	34
3	M	8 (died age 34· pancreatic cancer)	26
4	F	17 (died age 41: fallopian tube cancer)	24
5	F	18, 22, 26	19
6	F	11, 11, 18, 18	16
7	F	25, 37 (died age 53: ovarian cancer)	16
8	F	27	14
9	M	15, 16, 17, 18, 22	13
10	M	17, 17, 17, 33*	11
11	M	2, 7, 17	7
12	M	19	7
13	M	10, 10, 12, 21, 23*, 40	6
14	M	15, 20, 22	6
15	F	18	5
16	F	39	5
17	M	2, 17	5
18	F	3, 14	4
19	M	29, 31, 50	3
20	F	18	3
21	F	5, 11	3
22	M	5,16	3
23	F	7, 15	2

* Small bowel inspected with rigid endoscope

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Table 2 *The effect of small bowel endoscopy on polyp yield*

Patient No.	Sex	Age (years)	Number of polyps found by palpation or by transillumination (method of removal)	Number of additional polyps found by enteroscopy (method of removal	Post-operative follow-up (months)
1	F	4	3 (enterotomy)	1 (snare)	24
2	M	21	14 (enterotomy)	6 (snare)	12
3	F	19	6 (snare)	0	12
4	F	6	3 (enterotomy 2, snare 1)	2 (snare)	9
5	M	20	2 (enterotomy)	8 (snare 2, biopsy 6)	6
Total			28	17	

laparotomies were performed in other hospitals. Small bowel endoscopy using a rigid sigmoidoscope had been performed from the duodenojejunal flexure to the ileocaecal valve in two patients.

Peroperative enteroscopy study

The endoscope was passed through the mouth in three patients and through an enterotomy (which was necessary for the removal of polyps that were too large and broad based to be removed endoscopically) in two patients. Peroperative enteroscopy identified 17 polyps in the five patients which would otherwise have been overlooked (*Table 2*), which represents 38 per cent of all the polyps identified. These were of significant size since 11 of them required the diathermy snare to be used for their removal. In addition, seven patients had polyps which were obvious to the abdominal operator but which could be snared, thus avoiding additional enterotomies. The mean operating time was 3 h (range 2·5–3·5 h).

All patients made an uncomplicated recovery. The average postoperative ileus lasted 4 days (range 3–5 days). There were no wound infections and the postoperative stay averaged 10 days (range 7–11 days).

Discussion

The technique of peroperative enteroscopy has been described in patients with the Peutz–Jeghers syndrome[5] and in patients with familial adenomatous polyposis[6,7]. However, a comparison has not been made between a conventional approach and the operative use of an endoscope. The finding that the majority of repeat laparotomies were done because of polyp-induced complications suggests that conventional methods of identifying small bowel polyps at operation by external palpation and transillumination were inadequate.

In the 23 patients in the first part of this study there were four (17 per cent) on whom more than one laparotomy was conducted within a year. This implies that polyps were left behind at their earlier operations rather than that there was a fast rate of polyp regrowth. Such a view is further supported by the large number of additional polyps (17 or 38 per cent) found by employing enteroscopy in the five patients who form the second part of this report. Most of these polyps were sufficiently large in size to warrant diathermy snare removal. We believe that operative enteroscopy should reduce the early re-laparotomy rate.

An additional advantage of the use of an endoscope is the ability to remove some of the otherwise obvious polyps without making further enterotomies, although this can at times also be achieved by extensive eversion of the lumen of the bowel. Diathermy snaring of the more broadly based polyps may lead to noticeable heating of tissue, in which case serosal imbricating sutures may be inserted.

We have found it easier to pass a gastroscope through an enterotomy rather than to pass the paediatric colonoscope through the mouth. The stomach tends to loop with the latter technique and the delivery of the end of the colonoscope from the second part of the duodenum round to the first part of the jejunum can be awkward. Other difficulties with the technique are: the stomach may distend greatly with gas unless a nasogastric tube has been inserted separately; the small bowel mesentery may become quite stretched; and there is a tendency for the bowel to slip off the end of the instrument unless care is taken.

Experience of operating on patients with the Peutz–Jeghers syndrome is limited. We have shown that polyps may be overlooked and that the use of an endoscope to examine the whole of the bowel leads to a marked increase in the number of polyps found. We recommend peroperative enteroscopy as an adjunct when operating on patients with the Peutz–Jeghers syndrome.

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Pancreatic denervation for pain relief in chronic alcohol associated pancreatitis

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To denervate the pancreas of sensory afferents, 15 patients with intractable pain of chronic alcohol induced pancreatitis underwent left transthoracic splanchnicectomy with concomitant bilateral truncal vagotomy. All were malnourished and 11 were addicted to opiates. No respite had been obtained from 33 previous operative procedures. Each patient experienced almost immediate pain relief. Five, however, later had return of pain, but only to the right epigastrium. These five then underwent right transthoracic splanchnicectomy, after which four noted complete and apparently permanent disappearance of pain. In those 14 with a successful outcome there has been a 29 per cent mean increase in body weight, break of hard drug addition in ten of the 11 so afflicted, and return to gainful work or a relatively normal lifestyle in all 14 at a mean follow-up of 16 months. Although 11 of the 14 do have delayed gastric emptying, only one has required a drainage procedure. There have been no other late complications. This approach for control of incapacitating pain in chronic pancreatitis is both safe and simple and at the same time it appears to be reasonably reliable.

Keywords: Chronic pancreatitis, intractable pain, pancreatic denervation, transthoracic splanchnicectomy

Once established, chronic pancreatitis rarely precipitates an acute crisis that might warrant urgent surgery[1]. Its real threat is a protracted and unremitting drain on patient nutrition which in turn leads to such severe debilitation that life expectancy is significantly shortened with a poor quality of life. The pain provides an additional burden and the patient tries one therapy after another until addiction to opiates characterizes the final stage.

Many methods of providing pain relief have been advocated. These include non-addicting analgesic drugs, pancreatic duct decompression[2–4], partial or complete pancreatic resection[5–9] and pancreatic denervation[10–12]. No one approach is uniformly successful without causing some degree of permanent major morbidity, imposing a high risk of operative mortality, or often both. The major differences in outcome between these procedures have been in duration of pain relief when and if it is achieved and the price to be paid for such benefit in terms of immediate mortality and long-term morbidity.

For patients who have not gained a lasting pain-free state from pancreatic duct decompression or for those whose pancreatic ducts are not appropriately dilated a choice must be made between total to near-total pancreatectomy and pancreatic denervation. The latter procedure presents a less morbid subsequent course with a low surgical mortality rate.

Patients and methods

Patients

Of 21 patients seen for control of intractable pain due to chronic alcohol induced pancreatitis, 15 initially were considered to be good candidates for a denervation procedure. Two of these patients, however, refused operation. Five other patients had segmental dilatations of the main pancreatic duct on endoscopic retrograde pancreatography and therefore were deemed to qualify instead for a lateral pancreaticojejunostomy as described by Puestow and Gillesby[3]. Two of these five failed to obtain the desired pain relief and subsequently were offered pancreatic denervation. The final patient had such severe psychiatric problems that true evaluation of the denervation procedure was believed to be impossible and accordingly operation was not advised.

Ten men and five women were selected for pancreatic denervation. Their ages ranged from 22 to 57 years, with a mean of 41 years. They had a mean of 18 years of alcohol abuse, with a range of 7–29 years. Between two and 21 attacks of acute alcohol induced pancreatitis had been documented, with a mean of almost eight episodes for each patient. A history of recurrent bouts extended for as brief a time as 1 year and for as long as 17 years. The mean duration of recurrent attacks was 8 years. Eleven of the 15 had been addicted to opiates for between 2 and 9 years, with a mean of just over 4 years.

Eleven patients had diabetes mellitus. Four required insulin and two were managed on diet, while five essentially refused to participate in any efforts at control. All the patients were malnourished, weighing a mean of 22 per cent less than ideal for age, sex and height. The weight deficit varied between eight and 47 per cent of ideal. Pain was so severe on oral ingestion of a diet that one patient had been totally dependent on parenteral nutrition for >1 year.

All 15 patients had undergone at least one previous operative procedure for pain relief. Of the total 31 operations, 13 were lateral pancreaticojejunostomies[3], 11 were some form of internal drainage of a pseudocyst, six involved transduodenal sphincteroplasty and three were distal resections of the pancreas up to an estimated 70 per cent of gland mass. In addition, five patients had received from one to 13 coeliac ganglion blocks, with a mean of four per patient. Two of these patients had obtained temporary relief for as long as 3 months, yet after the third or fourth block, benefit lasted at most for 1–2 days.

Each patient subjected to the pancreatic denervation procedure had undergone preoperative computed abdominal tomography and endoscopic retrograde cholangiopancreatography. Neither study demonstrated an undrained ectatic pancreatic duct or pseudocyst of >2 cm diameter in any of the patients. No patient had symptoms or clinical findings suggestive of common bile duct or duodenal obstruction, ascites or gastrointestinal bleeding. Pancreatic malignancy could not be excluded with absolute certainty but absence of duodenal and bile duct obstruction and the absence of a finite pancreatic mass on computed tomography were taken to rule out such a possibility.

Operative procedure

The transthoracic approach to pancreatic denervation was used because of reported inconsistent results with transabdominal and extraperitoneal coeliac ganglionectomy and only short-term benefit from coeliac ganglion blocks. A left-sided thoracotomy was used for the initial operation to make concomitant bilateral truncal vagotomy technically easier. The Clinical Trials Committee of Emory University School of Medicine, where the study was started, suggested that bilateral truncal vagotomy should be included because of the noted reduction in

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incidence of recurrent attacks of alcohol induced pancreatitis following this procedure[13] Division of the nerves proximally assured a more complete denervation and avoided the need to dissect in tissues extensively scarred by previous pancreatic inflammation, operation or nerve block injection.

With the patient in the right lateral position, a left posterolateral thoracotomy was performed through either the seventh intercostal space or through the bed of the seventh rib. To guarantee easy identification of the splanchnic nerves and to avoid injury to the corresponding sympathetic ganglia, a generous incision was considered to be an absolute necessity

The greater and lesser splanchnic nerve plexuses were noted to pass inferiorly from their respective thoracic ganglia in first a medial and then an anterior direction After the posterior parietal pleura had been incised, the plexus of the greater splanchnic nerve (generally with branches arising from as high as the fifth thoracic sympathetic ganglion and as low as the tenth) was clipped at its origin, divided and then traced down to the diaphragm, where it was clipped and divided again. A similar technique was used for the lesser splanchnic nerve (usually involving branch excision from the ninth to the 11th thoracic ganglia). Only twice was the lesser splanchnic nerve identified with certainty Care was taken not to damage any of the sympathetic ganglia or their interconnecting trunks. A standard bilateral truncal vagotomy was carried out

The pleura was left open and the chest was routinely closed without drainage. Four patients had obvious retropleural chronic oedema and scarring and because of serous drainage from the pleural incisions, one patient required closed thoracotomy tube drainage in the recovery room. The other three patients, therefore, had chest tubes inserted prophylactically The tubes were removed without subsequent incident on the second postoperative day. For those patients requiring right transthoracic splanchnicectomy, an identical procedure was carried out

The mean duration of surgery was 41 min, with a range of 32 to 59 min There were no immediate operative or postoperative complications. Blood transfusion was not needed. Hospitalization varied from 4 to 13 days, with a mean of 7 days, if one patient with insurmountable psychiatric problems is excluded There were no deaths.

Results

Each of the 15 patients experienced immediate and complete relief from their abdominal and back pain following left greater and lesser splanchnicectomy with bilateral truncal vagotomy. Five, however, noted a return of the pain confined to the right side of the epigastrium. Pain recurrence was sudden on the fourth postoperative day in the woman patient with severe psychiatric problems, and she was considered to represent a poor candidate for the denervation procedure. The other four patients had a gradual return of pain beginning at 3–8 months after the first operation. Within a further 3–4 months the recurrent pain was so severe as to justify right greater and lesser splanchnicectomy. Four of the five patients then gained immediate and apparently permanent pain relief. The one exception was the psychotic woman who had obtained only a 4-day respite following the first operation. The second procedure caused no change in her pain pattern and surgery was assumed to have been of no benefit

On a follow-up ranging from 5 to 28 months, with an average of 16 months, the 14 successful patients remained pain-free after unilateral denervation alone in ten cases and bilateral operation in four cases. The woman who had obtained no benefit died many months later still dependent upon total parenteral nutrition. The only other known death occurred at 11 months as a result of a high-speed automobile collision.

Excluding the psychotic patient who obtained no pain benefit, there was a 29 per cent mean increase in body-weight over the preoperative weight, with a range of 11 to 41 per cent. Ten of the 11 patients broke their addiction to opiates and one has returned to making his livelihood as an illicit hard drug dealer. If that way of life is taken to represent self-sufficiency(!) then all 14 were gainfully employed at last contact. Thirteen have resumed varying degrees of alcohol abuse.

The only late complication has been delayed gastric emptying. This was confirmed by barium or isotope studies in 11 patients Symptoms have been sufficiently troublesome to require a draining pyloroplasty in only one patient.

Discussion

The role of surgery is limited in chronic pancreatitis[1]. Metabolic derangements arise because of pancreatic insufficiency, both exocrine and endocrine, and dietary restrictions, specific vitamin, mineral and digestive supplements and occasionally insulin regulation of an accompanying diabetes mellitus become dominant considerations. Approximately 10 per cent of patients with chronic pancreatitis will develop one or more complication requiring surgical correction. common duct and/or duodenal obstruction due to pancreatic cicatrix, pseudocyst formation, a leaking pancreatic duct causing ascites or splenic vein thrombosis. Other complications relate to alcohol abuse and choledocholithiasis.

An unremitting supraumbilical pain, boring into the back, made worse by eating characterizes the syndrome. Various analgesics become less and less effective and addiction to opiates may become the most prominent feature.

Before the pain becomes refractory to analgesics, the identification of an anatomical lesion is always indicated[1,4]. Once defined, its surgical correction is an important part of the strategy for pain control.

First to be considered is the possibility of pancreatic duct obstruction or a pancreatic pseudocyst[1,4]. The results of surgical decompression, however, are not uniformly good[1–4]; one-third of patients obtain complete relief, one-third are considerably improved and one-third never experience any benefit.

For those patients who fail to gain relief from a drainage procedure or in whom no dilated duct or pancreatic fluid collection can be delineated, a choice must then be made between surgical ablation of all or a part of the gland and some method of pancreatic denervation.

Results obtained from pancreatic resection correlate well with the percentage of the organ excised[5–8] (*Table 1*). At the range of 80–95 per cent resection, almost 90 per cent of patients eventually become pain-free[6,7]. Beyond this amount of excision, results worsen[5,9,14]. Complications relate to the brittle diabetic state created by complete removal of the pancreas and those arising from the anastomosis between the common bile duct and the alimentary tract.

Pancreatic denervation provides an alternative approach[15–17] but pain control by coeliac ganglion blocks becomes less complete and lasts for shorter periods with the passage of time[18–21]. After a fifth or sixth session, the pain pattern is seldom modified for longer than 1–2 days, and coeliac ganglionectomy may be carried out[10,11]. With the exception of consistently good results obtained at one clinic[10], true benefit has been reported in only about half of the documented cases[11] and this lack of reliability has reduced enthusiasm for the procedure. Incomplete ganglion excision, failure to divide all of the responsible pain fibres and nerve regeneration may well account for variable results. To avoid these possibilities it has been suggested that the pancreas be converted into a denervated free flap[22] but this represents a major surgical undertaking and its reliability and duration of benefit are uncertain

Since the greater and lesser splanchnic nerves contain afferent fibres specifically from foregut and midgut organs, a

Table 1 *Pancreatectomy for pain relief in chronic pancreatitis*

		Pain relief		
Extent of resection (%)	Total (*n*)	Excellent (*n*)	Good (*n*)	Fair/poor (*n*)
<40	40	20	6	14
40–80	98	75	6	17
80–95	124	110	–	14
Total (100)	24	10	2	12

Data from selected published reports[5–8]

Table 2 *Left splanchnicectomy for pain relief in chronic pancreatitis*

	Pain relief			
Splanchnicectomy	Total (*n*)	Excellent (*n*)	Good (*n*)	Fair/poor (*n*)
Left alone	10	9	1	–
Left plus thoracic sympathectomy	8	4	3	1
Left plus coeliac ganglionectomy	39	19	–	20
Total left splanchnicectomies	57	32	4	21

Data cited in published reports[10–12,23–29]

Table 3 *Bilateral splanchnicectomy for pain relief in chronic pancreatitis*

	Pain relief			
Splanchnicectomy	Total (*n*)	Excellent (*n*)	Good (*n*)	Fair/poor (*n*)
Bilateral alone	0	–	–	–
Bilateral plus thoracic sympathectomy	20	17	1	2
Bilateral plus coeliac ganglionectomy	10	8	0	2
Total bilateral	30	25	1	4

Data cited in published reports[10–12,23–29]

transthoracic approach would appear to be a reasonable way to accomplish the desired denervation[12,14–17]. Other than a small series of right splanchnicectomies with indifferent results, the majority of reports describe either a left or a bilateral splanchnicectomy, usually coupled with a thoracic sympathectomy or a coeliac ganglionectomy[10–12,23–29] (*Tables 2* and *3*). Since the procedures were carried out transabdominally or through a confined flank incision, how totally the splanchnicectomy is done is open to question.

Results obtained from the present study suggest that left transthoracic splanchnicectomy offers a chance for permanent freedom from pain in approximately two-thirds of patients. If pain returns then a similar right-sided denervation might provide a lasting pain-free state.

The role of vagotomy is unclear. Because of the uncertainty that all pain fibres pass along the splanchnic nerves and because of the documented decreased incidence of recurrent attacks of alcohol induced pancreatitis following bilateral truncal vagotomy[13], this additional component to the operation seems worthwhile.

The late consequences of splanchnicectomy and a bilateral truncal vagotomy are unknown. Delayed gastric emptying occurred in most patients but in only one did surgical intervention become necessary. The postoperative morbidity rate associated with pancreatic denervation is significantly less than that following a total or a near total pancreatectomy.

In conclusion, denervation of the pancreas via a transthoracic splanchnicectomy appears to offer relief from the incapacitating pain of chronic alcohol induced pancreatitis. It is indicated for those individuals who have failed to gain relief from an appropriate internal drainage procedure or whose pancreatic duct system is not sufficiently dilated.

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Progressive pneumoperitoneum in the management of giant incisional hernias: a study of 41 patients

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Forty-one patients (17 men and 24 women) were treated with progressive pneumoperitoneum before repair of giant incisional hernias. The pneumoperitoneum was induced using nitrous oxide gas and a laparoscopic insufflator, and was topped up every other day for a mean of 5·5 days with a total injection of 23·2 litres of nitrous oxide. The pneumoperitoneum was well tolerated in 30 patients, caused a mild temporary pain in 10 patients and a sharp pain in one patient; no serious side-effects occurred. All the patients underwent surgery to repair their hernias, 40 patients were available for follow-up for a mean of 25·3 months, only two hernias recurred both within 4 months of the operation.

Keywords: Hernia, pneumoperitoneum

The technique of progressive pneumoperitoneum before repair of giant hernias of the abdominal wall was first described by Goni Moreno in 1947[1]. Koontz and Graves in 1954[2] described their experience of the technique and other authors have more recently recommended it[3–12].

The pathophysiology of giant abdominal hernias includes a reduction in the capacity of the abdominal cavity and contracture of the abdominal flank muscles; poor pulmonary function and impaired venous return are consequences of the reduced abdominal muscular contribution to respiratory movements. The pneumoperitoneum progressively enlarges the abdominal cavity, stretches the abdominal muscles allowing an increased respiratory excursion and has an adhesiolytic effect which makes dissection and subsequent reduction of hernial contents easier.

We have used this technique in 41 patients and report our experience.

Patients and methods

Forty-one patients (17 men and 24 women) with giant incisional hernias were treated with the technique of progressive pneumoperitoneum at the Laparoscopy Unit of Padua between December 1979 and March 1988. Their age ranged from 42 to 73 years, the mean age was 58·5 years. Thirteen patients had undergone one or more previous operations to repair their hernias. Three patients presented with incarcerated hernias.The hernial sac diameters ranged from a minimum of 15 cm in breadth and 10 cm in length to a maximum of 40 cm × 30 cm; with mean diameters of 20 cm × 6 cm × 17·3 cm; the diameter of the hernia neck measured from 5 cm to 15 cm. Thirty-five hernias were median, four were pararectal and two were subcostal.

The pneumoperitoneum sessions were carried out every other day introducing nitrous oxide with an automatic insufflator designed for laparoscopy The gas was introduced in nine cases with a Veress needle (diameter 1·8 mm) inserted under local anaesthesia, in four cases with a spinal needle (diameter 1·1 mm) and in 28 cases with an endoperitoneal catheter (diameter 1·2 mm) introduced and kept in position for the duration of the pneumoperitoneum

Generally the catheter was inserted in the left iliac region, but when the hernia was very large every other site on the abdominal wall with sound tissues was used

The duration of the pneumoperitoneum ranged from a minimum of 6 to a maximum of 16 days with a mean of 10·5 days, the pneumoperitoneum sessions, carried out every other day, ranged from 4 to 8 days with a mean of 5·5 days

The volume of nitrous oxide introduced at each session was 1000–1500 ml greater than the previous session and depended on the patient's subjective feeling of abdominal tension and on the increase in pressure registered by the nitrous oxide insufflator. The final amount of nitrous oxide introduced at the end of the treatment ranged from 9 to 38·5 litres with a mean of 23·2 litres All the patients except one were followed up after repair of their hernia (range 6 months to 9 years with a mean of 25·3 months)

Results

The progressive pneumoperitoneum was comfortably tolerated by 30 patients (73 per cent), 10 patients (24 per cent) suffered mild shoulder tip pain only during the first session. Nevertheless one patient with an incarcerated hernia suffered distressing pain which prevented further pneumoperitoneum. No serious accidents occurred – in one patient the endoperitoneal catheter came out and it was necessary to reinsert it, in another case the catheter completely entered the peritoneal cavity and was removed at operation without any septic complications, on another occasion moderate arterial bleeding occurred at the insertion point and a small haemoperitoneum was found during surgical repair.

Hernia repair utilized Dacron® mesh (Meadox Medical Inc., New Jersey, USA) in 16 patients, 20 patients had their hernias repaired by musculoaponeurotic apposition without overlap and five patients underwent musculoaponeurotic repair with double-breasting of the layers. Vicryl® (Ethicon Ltd., Edinburgh, UK) or Dexon® (Davis and Geck, Gosport, UK) were used as sutures. There were no intraoperative surgical complications. In three patients, two of whom had undergone a repair with Dacron mesh, the wound suppurated after the repair and healed with medical therapy. All the patients treated except one were followed up (range 6 months to 9 years with a mean of 25·3 months). Relapses were observed in two of the 40 patients – in the first patient, who had undergone a double-breasted plastic operation, the relapse was observed after 1 month, whereas in the other patient, who had undergone a plastic operation with reinforcement mesh, the wound suppurated and a 5 cm long recurrent hernia was observed 4 months after surgery.

Discussion

There are numerous reports that pneumoperitoneum facilitates the repair of giant incisional hernias because it allows suturing of the defect under less tension[1–10,12–14]. Although this advantage has been claimed for the technique it has not been possible to measure it. Improvements in respiratory function,

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spirometry, venous blood flow and abdominal electromyography claimed by some authors[1,6,12] have not been confirmed by others. However, all the reports agree that this method of preparation for giant hernia repair substantially reduces the duration of the operation, the incidence of postoperative complications and the recurrence rate after surgery[1–12].

In the series reported here the pneumoperitoneum was induced differently from previous reported series, with the use of laparoscopic insufflation being novel and simple. Nitrous oxide is the preferred gas; although it is reabsorbed faster than air it is non-toxic and is conveniently available in most hospitals where laparoscopy is performed. It can be introduced by an automatic insufflator that indicates exactly the quantity of introduced litres and the insufflation abdominal pressure. The laparoscopic insufflation is a useful calibrated method to measure the volume of gas introduced and the abdominal tension. The rapid reabsorption of nitrous oxide explains the necessity to top up the volume every other day and the large total volume of gas used in most cases.

Originally, in the first nine patients, we introduced the gas through a Veress needle (diameter 1·8 mm) inserted at each session under local anaesthesia, and then in four cases a spinal needle (diameter 1·1 mm) was introduced each time. Although there were no accidents with these instruments they required to be inserted afresh at each session. The employment in the last 28 cases of a small endoperitoneal catheter (diameter 1·2 mm) introduced with a removable mandrel and kept in position for the whole duration proved to be effective because it is handier, less dangerous and more acceptable to the patients.

The trivial complications observed in this study confirm what is reported in the literature[7,9–11,13,14] The treatment was very well tolerated in 73 per cent of cases, caused a mild temporary pain radiating to the shoulders in 24 per cent and a sharp persistent pain with subsequent break of the treatment in one case of incarcerated giant hernia (2 per cent). These results are similar to those reported by others[2–5,9]. It is important to point out the low percentage of relapses (5 per cent; 2 out of 41 cases) with a mean follow-up of 25·3 months. This result is relevant because it is known[11] that the incidence of relapses after repair of giant hernia is generally high, particularly in the first 6 months of follow-up.

In conclusion the technique of pneumoperitoneum before repair of giant abdominal hernias causes an increase in the abdominal cavity volume, it improves respiratory dynamics and venous return, and it reduces the abdominal wall muscular tension. For all these reasons it facilitates the surgical technique and reduces the percentage of long term recurrences. The treatment may be carried out without hospitalization and, moreover, it is safe and is recommended for the elderly and patients with significant cardiorespiratory comorbidity

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Short note

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Femoral hernia: an avoidable source of surgical mortality

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Femoral hernias account for less than 10 per cent of all groin hernias[1]; however, in British practice 40 per cent of these hernias present as emergencies with strangulation or incarceration[2], and despite improvements in surgery and anaesthesia the management of strangulated femoral hernias continues to be a source of perioperative morbidity and mortality not associated with elective femoral hernia repair[3]. The reasons for this excess morbidity and mortality are not entirely clear; to clarify these issues we have audited our experience.

Patients and methods

In an 11-year period, between January 1976 and December 1987, 145 patients (38 male, 107 female) with 146 hernias (99 right, 47 left) underwent femoral hernia repair at North Tees General Hospital. Sixty-three patients presented as emergencies and had urgent surgery, and 82 patients had elective femoral hernia repair Nineteen patients had a synchronous ipsilateral inguinal hernia and 11 patients had had an ipsilateral inguinal hernia repaired previously[4]

In the elective group all but one patient had been aware of the presence of a groin lump for more than 1 month, and this had been symptomatic in 95 per cent of these patients. Only 27 (43 per cent) of the patients presenting as an emergency had been aware of a lump in the groin for more than 1 month.

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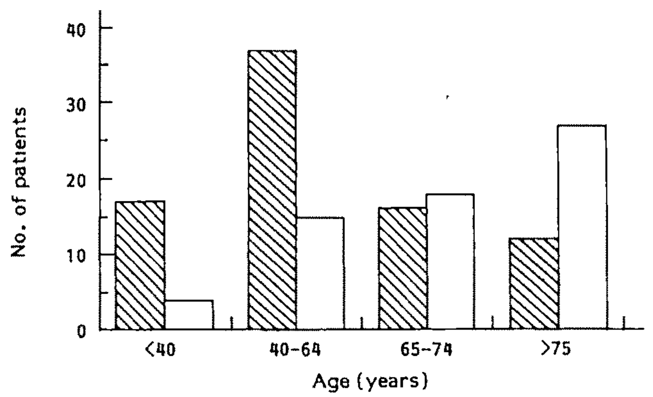

Figure 1 *Age distribution of patients with femoral hernia undergoing emergency* (□) *or elective* (■) *repair*

Results

The most significant difference between the emergency group and the elective group was age· 43 (68 per cent) patients in the emergency group were aged over 65 years compared with only 25 (30 per cent) of those having elective repair ($P<0{\cdot}0001$) (*Figure 1*). The group of patients presenting as an emergency had a higher incidence of coexisting pathology (*Table 1*); 58 per cent of the patients in the emergency group presented with symptoms of intestinal obstruction. Urinary catheters and prophylactic antibiotics against bowel organisms were employed in the emergency group. Less than 7 per cent of the patients presenting as emergencies were in hospital for more than 24 h before surgery.

All but three patients underwent repair under general anaesthesia. The preferred operation for the elective cases was the low or Lockwood operation (57 of 82 cases). In the emergencies, the preperitoneal (McEvedy/Henry) operation was used in just under half of the cases None of the patients undergoing elective repair required bowel resection, in contrast to 22 of the 63 patients undergoing urgent repair Drains were used if bowel was resected. The preferred suture material in all cases was monofilament polypropylene (Prolene®, Ethicon Ltd., Edinburgh, UK).

Morbidity following elective repair was extremely low and no patients died. The morbidity rate after urgent repair was significantly higher (wound infection 17 per cent, chest infection 9 per cent, pulmonary embolism 5 per cent, septicaemia 3 per cent). Five patients in the emergency group died (8 per cent) giving an overall mortality rate of 3·4 per cent. Three patients died as a result of massive pulmonary embolism, and one patient died from a postoperative stroke. One other patient died from infective complications.

Follow-up data were available for 125 patients (86 per cent). At a median follow-up of two years, five patients (3 4 per cent) had suffered a recurrence (considered to be an ipsilateral groin hernia). Three of these recurrences were direct inguinal hernias following the use of the inguinal operation.

Discussion

An overall mortality rate of 3·4 per cent (8 per cent of emergency patients) compares favourably with other reported studies[5]. The greater age of the emergency patients and their coexisting disease contributed to this mortality rate. The commonest cause of death was massive pulmonary embolism and these deaths occurred before the use of low-dose subcutaneous heparin became routine. The three recurrences after the inguinal repair highlight the need for an effective repair of the posterior wall of the inguinal canal when this approach is used.

Table 1 *Coexisting medical morbidity (63 emergency cases)*

	No of patients
Respiratory (e.g. chronic obstructive airways disease, emphysema)	12 (19)
Cardiac (e.g angina, previous myocardial infarction)	25 (40)
Neurological (e.g previous stroke, Parkinson's disease)	6 (10)
Endocrine (e.g. diabetes mellitus)	5 (8)
Alimentary (e.g diverticular disease, previous carcinoma colon)	19 (30)
Musculoskeletal	10 (16)

Figures in parentheses are percentages

This study has highlighted the problems of patients who delay in seeking medical advice The accuracy of initial diagnosis from the referring practitioner was only 35 per cent in this series. This contributes to a further delay in seeking expert opinion. In a recent study, more than 62 per cent of general practitioners and more than 20 per cent of consultant general surgeons would not recommend repair of an asymptomatic femoral hernia in an elderly woman[6] even though all reported series show a very low mortality rate for elective repair We recommend a policy whereby all patients with groin hernias, particularly those with femoral hernia, are offered elective surgery with its associated low morbidity rate and negligible mortality rate rather than exposing the patient to the risk of a complication necessitating emergency repair with its consequent higher morbidity and risk of mortality[7]. The argument that pre-existing medical problems and advanced age *per se* preclude elective surgery is no longer valid in the era of modern surgical and anaesthetic practice[8].

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Indications for conservative management of acute scrotal pain in children

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Forty-three boys who presented with acute scrotal pain were studied retrospectively. Of these, 40 had torsion of scrotal contents. Torsion of testicular appendages, a self limiting condition, tended to present later than testicular torsion ($P = 0{\cdot}002$)*. The testis was saved in all 11 cases of testicular torsion explored within 12 h of the onset of pain but orchidectomy was required in four who presented later. In 11 cases, a torted testicular appendage diagnosed as a tender nodule was found on examining the upper pole of the testis. The remaining 14 cases of torted appendage were diagnosed at operation because testicular torsion could not be excluded due to scrotal swelling. Most* (*12*) *of this operated group were not seen until 3 days after the onset of pain. This study suggested that urgent operation was unnecessary in those in whom a tender nodule was found* (*pathognomonic of a torted appendage*) *and in those presenting after more than 24 h of pain with scrotal erythema and oedema. The likely diagnosis in the latter case is a torted appendage and in cases of torsion of the testis there is no prospect of salvage at this stage. These guidelines were applied to a group of 20 boys studied prospectively. In eight, all with less than 24 h of pain, immediate exploration was undertaken and testicular torsion was confirmed in six. The remaining 12 fulfilled the criteria for conservative management and were observed. All had normal testes at late review. Careful clinical assessment in boys with scrotal pain indicates which cases may be treated by non-operative management without fear of losing a salvageable testis.*

Keywords: Torsion of testis, torsion of testicular appendage, children, conservative management

In boys under 15 years of age, torsion of a testicular appendage (appendix testis or hydatid of Morgagni) is a more common cause of acute scrotal pain than testicular torsion[1,2] The former condition is self limiting but scrotal exploration has been advised in all such cases[3] However, a policy of non-operative management of torsion of the appendix testis has been advocated by Holland *et al*[4] who report relief from symptoms within 7 days.

Patients and methods

This investigation consisted of two separate studies, one retrospective and the other prospective

In the initial study, the case notes of 43 boys aged under 15 years of age who were admitted to this hospital with acute scrotal pain were examined. Particular note was taken of the initial and final diagnoses, duration of pain and physical signs. The results of this study suggested guidelines for the management of acute scrotal pain in this age group and these were assessed in a prospective study in the subsequent 20 cases Differences were analysed by the Mann–Whitney U test and the χ^2 test as appropriate

Results

Retrospective study

In these 43 cases, three boys had epididymitis which was diagnosed at exploration. Of the remaining 40, 15 boys had torsion of the testicle and 25 had a torted appendage. Both of these conditions were more common in boys over 10 years of age (*Table 1*) There was a marked peak age of 11–12 years for torsion of a testicular appendage, this being similar to the findings of others[2].

The initial clinical diagnosis and the final outcome in all cases of torsion of scrotal contents were analysed further with particular emphasis on the delay between the onset of pain and assessment in hospital (*Table 2*).

Boys with torsion of the testicle tended to present early (median 6 h) and three-quarters (11) were seen and explored within 12 h of the commencement of pain. In all cases, the testis was found to be viable and when reviewed between 4 and 6 weeks after operation none had atrophied The other four boys presented after at least 14 h of pain and in each case, although immediate exploration was undertaken, the testis was non-viable and orchidectomy was performed

The boys with torsion of a testicular appendage tended to present later (median 48 h, $P = 0{\cdot}002$), presumably because this condition is less painful. Nearly half (12) of those with a torted appendage gave a history of 3 or more days of continuous pain. In 11 cases, a clinical diagnosis of torsion of the hydatid was made on the basis of a tender nodule at the upper pole of the testis. Significantly, most of these boys (eight) were seen in hospital within 24 h of the onset of pain Rather more than half (six) of the clinically diagnosed group underwent immediate exploration and the preoperative diagnosis was confirmed in each case The other five in this group were treated conservatively, all being pain free within 1 week and none had testicular atrophy at later review.

The clinical findings in boys presenting late with testicular torsion or torted appendage are similar in that swelling, scrotal oedema and erythema make the conditions indistinguishable on clinical grounds (*Table 3*). In the remaining 14 cases of torsion of a testicular appendage, torsion of the testicle could not be excluded clinically and the correct diagnoses were made at urgent exploration. Interestingly, only three from this group of 14 were seen within 24 h of the onset of pain and, of the remainder, ten had experienced continuous pain of over 3 days' duration.

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Prospective study

From the initial study and review of the literature, it was evident that torsion of a testicular appendage was a self limiting condition which did not require surgery. A strategy was therefore evolved for the management of acute scrotal pain in boys based on the clinical findings and the duration of pain. Urgent operation was to be undertaken in all cases with less than 24 h of pain, unless a palpable tender nodule was present, in which case the management was conservative When there had been continuous pain for more than 24 h, a policy of observation was adopted as experience had shown that the majority of such cases were torted appendages and if the correct diagnosis was testicular torsion there was no prospect of testicular salvage.

This policy was applied to the next 20 cases. One half gave a history of less than 24 h and the other half a history of over 24 h (*Table 4*). Of the ten boys who gave a history of less than 24 h of pain the clinical diagnosis was torsion of the testis in six. In each case this was confirmed at operation and in three of these the testis was infarcted and orchidectomy was required These boys reported pain of 6, 18 and 20 h duration.

In a further two boys, presenting at 8 and 24 h, torsion of the testicle could not be excluded and immediate exploration was undertaken at which time a torted appendage was diagnosed. The remaining two boys with a less than 24 h history had palpable tender nodules, and torted hydatids were diagnosed. Both were treated conservatively

Ten boys were admitted with a history of at least 24 h of pain. In one (pain for 27 h), a tender nodule was palpable and in the remainder (pain for 3–5 days) the scrotum was swollen, red and tender making palpation difficult. All of these boys were treated by non-operative management. In the 12 boys treated conservatively there was complete resolution of symptoms within 1 week of onset and all had normal testes at review 4–6 weeks later.

Table 1 *Age of boys with torsion of scrotal contents retrospective study*

	Age (years)									
	<5	6	7	8	9	10	11	12	13	14
Torsion of testis	2	2	1	0	1	0	1	2	4	2
Torted appendage	0	2	0	2	1	3	9	6	2	0

Table 2 *Duration of pain retrospective study*

	Duration of pain					
	<6 h	6–12 h	12–18 h	18–24 h	24–28 h	>3 days
Torsion of testis ($n=15$)	9	2	2	1	0	1
Torted appendage ($n=25$)	3	5	2	1	2	12

Discussion

Torsion of the testis is a surgical emergency and no time should be lost in performing urgent exploration. The testicular salvage rate falls from 80 per cent if the testis is explored within 5 h of the onset of pain to 20 per cent if symptoms have been present for over 10 h, and after 24 h all testes have been said to be non-viable[5]. In addition, testicular atrophy has been shown to be inevitable if torsion has been present for 8–12 h[1,6].

A policy of conservative management can only be advocated if cases of torted testes that can be salvaged can be confidently excluded. The clinical diagnosis of epididymo-orchitis in males under 25 years of age may be unsafe[7] and operation is therefore mandatory whenever any doubt exists as to the diagnosis in boys with scrotal pain of less than 24 h duration.

The findings in the present studies confirm those of others[1,2,4] that in a proportion of cases, a clear-cut clinical diagnosis of torsion of a testicular appendage can be made. Under these circumstances a conservative approach can safely be adopted. It is our experience that when boys with torsion of an appendage are examined within 24 h of the onset of symptoms, in most cases the typical features of this condition are apparent, i.e. normal lie of the testis, absence of testicular tenderness and a tender nodule at the upper pole which is sometimes visible as a blue swelling.

In the retrospective series, most of the boys with torsion of an appendage who presented late (>24 h) underwent exploration and in all cases, although the patients were systemically well, examination revealed a tender, swollen, red scrotum and thus torsion was suspected. These testes had a normal lie within the scrotum but nodules could not be palpated. At operation, we have found the salient features of torsion of the appendix testis of a few days' standing to be a secondary hydrocele containing turbid fluid, an infarcted testicular appendage and a normal testis.

In this study, all those with testicular torsion presenting with a history of more than 14 h of continuous pain had non-viable testes. Indeed, Knight and Vassy[8] report that when torsion of

Table 4 *Duration of pain: prospective study*

	Duration of pain					
	<6 h	6–12 h	12–18 h	18–24 h	24–28 h	>3 days
Torsion of testis ($n=6$)	2	2	1	1	0	0
Torted appendage ($n=14$)	1	1	1	1	1	9

Table 3 *Scrotal findings in boys with torsion of scrotal contents and influence of duration of symptoms*

	Torsion of testis	Torsion of testicular appendage (all cases)	Torsion of testicular appendage	
			Duration <24 h	Duration >24 h
Number	21	39	15	24
Erythema	10 (48)*	25 (64)*	3 (20)	22 (92)
Swelling	13 (62)*	25 (64)*	4 (27)	21 (88)
Elevated lie	10 (48)†	4 (10)†	1 (7)	3 (13)
Tender nodule	0†	14 (36)†	10 (67)	4 (17)

Values are numbers of cases with percentage in parenthesis; * not significant; † $P<0.01$, Mann–Whitney *U* test the testis is associated with continuous pain of more than 12 h duration along with scrotal erythema and oedema the testis is not viable, but these clinical features are also those of delayed presentation of torsion of testicular appendages.

Although the scrotum should undoubtedly be explored when there is any prospect of salvaging a testicular torsion, we have clear evidence to support a conservative approach in those presenting with a history of continuous pain extending beyond 24 h. Urgent exploration is mandatory in all cases of testicular torsion of less than 24 h duration and similarly in all cases where the surgeon is in doubt

Boys with an obvious torsion and a non-viable testis (history >24 h) should undergo orchidectomy for symptomatic relief and fixation of the contralateral testis with unabsorbable sutures. This avoids any danger of an infarcted testis sloughing later. Those in whom a tender palpable nodule is present have torsion of a testicular appendage and can be treated conservatively The parents are warned that there may be an increase in the swelling over the following days but that complete resolution can be anticipated within 1 week.

Boys presenting with more than 24 h of continuous pain along with scrotal erythema and oedema are likely to have a torted appendage and the remainder have a torted testis that cannot be salvaged after such a delay. These boys should be seen during the next few days to assess progress. If there is any doubt as to whether it is the testis or the appendage which has infarcted, Doppler flow studies or radionucleotide scanning[9] will indicate whether the testicle has a normal blood supply In the case of a non-viable testis, orchidectomy and contralateral testicular fixation are mandatory.

Persistent pain from a torted hydatid may occasionally necessitate excision[4] although this has not been our experience. In all cases, the patients and their parents are warned to report all new instances of scrotal pain. Torsion after previous fixation is not unknown and intermittent torsion is now recognized. Early elective orchidopexy has been recommended[10].

The measures outlined above would reduce the number of unnecessary emergency surgical procedures in boys with acute scrotal pain and decrease the occasions when routine lists are halted, other emergencies are delayed or boys are anaesthetized in less than ideal circumstances for fear of castration by neglect.

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Skeletal muscle enzyme activities and metabolic substrates during exercise in patients with postoperative fatigue

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Subjective fatigue was quantified before and 20 days after uncomplicated elective abdominal surgery in 12 patients and compared with changes in heart rate, enzyme activities and skeletal muscle substrates before and after bicycle exercise for 10 min at 65 per cent of patients' preoperative maximum work capacity. Fatigue increased from a mean(s.e.m.) preoperative level of 2·5(0·5) arbitrary units to 4·6(0·5) on postoperative day 20 ($P<0{\cdot}01$)*. Body-weight, triceps skinfold thickness and arm circumference decreased postoperatively* ($P<0{\cdot}02$)*. Postoperative values of muscle enzyme activities indicative of oxidative phosphorylation capacity (citrate synthase and 3-*OH*-acyl coenzyme A dehydrogenase) were lower than preoperative values* ($P<0{\cdot}05$)*. Lactate dehydrogenase was unaltered and resting values of muscle glycogen and adenosine triphosphate were higher after operation* ($P<0{\cdot}05$)*. In response to exercise, heart rate, muscle glucose, glucose-6-phosphate and lactate increased* ($P<0{\cdot}05$)*, while muscle glycogen and creatine phosphate decreased* ($P<0{\cdot}05$)*. Increase in postoperative fatigue correlated with the increase in heart rate* ($P<0{\cdot}05$)*, while no significant correlations were found between fatigue and muscle parameters. Our results suggest that lack of exercise and malnutrition may be of importance in the decrease in work capacity and in fatigue after operation.*

Keywords: Fatigue, abdominal surgery, skeletal muscle, enzymes, substrates, exercise

Increased fatigue after uncomplicated abdominal surgery correlates with deterioration of nutritional status[1] and with decrease in muscle force and endurance[2]. The purpose of this study was to investigate whether changes in postoperative fatigue were related to changes in the concentrations of substrates and metabolic intermediates, and in enzyme activities in skeletal muscle during exercise.

Patients and methods

Twelve patients, seven women and five men, aged 24–58 years (mean(s.e.m.) 43(3) years), scheduled for elective abdominal surgery were studied. None had liver, renal, heart, endocrine or psychiatric disease. Body-weight was stable within the 3 months before surgery. The type of operations were: repair of sliding oesophageal hernia (two), cholecystectomy (six), intestinal resection (three) and rectal amputation (one). All patients received general anaesthesia with halothane or low-dose fentanyl. Postoperative nutrition consisted of approximately 0·5 mol glucose daily for 2 days. No patient had a postoperative complication, and all had regular chest physiotherapy without special exercise rehabilitation.

All patients were examined twice before operation and 20 days after surgery by the same examiner. Studies were performed in the morning, with patients fasting overnight.

Fatigue

Subjective feeling of fatigue was assessed before the exercise test using a fatigue scale[3] which quantifies fatigue in arbitrary units from one (fit) to ten (fatigued).

Anthropometric measurements

Triceps skinfold thickness was measured with a Harpenden Skin-fold Caliper® on the posterior aspect of the arm halfway between the acromion process and olecranon. Midarm circumference was measured with a tape. At each examination a mean of six values, three from each arm, was taken. Arm muscle circumference was calculated from triceps skinfold thickness and arm circumference according to the formula arm muscle circumference = arm circumference (cm) − (0·314 × triceps skinfold thickness (mm)).

Exercise test

All patients had their preoperative physical capacity determined on a bicycle ergometer with a pedal frequency of 50 revolutions per min. The patients cycled in normal sitting position. The electrocardiogram was registered during the last 15 s of each min, and the heart rate was determined. At this initial preoperative examination, maximum working capacity was assessed as described by Åstrand and Rodahl[4], demanding at least 4 min of work at each of at least three workloads in order to attain steady-state heart rate. Based on these results, the exercise load to be used in the second preoperative test and in the postoperative test was calculated as the load eliciting 75 per cent of the individual's heart rate reserve plus heart rate at rest (heart rate reserve equals maximum heart rate minus heart rate at rest). This heart rate corresponds to about 65 per cent of the maximum work capacity[4]. At the second preoperative and at the postoperative test the patients exercised at this load (mean(s.e.m.) 108(10) W) for exactly 10 min.

Muscle biopsies

Needle biopsies[5] were obtained from the quadriceps femoris (vastus lateralis) muscle 20 cm above the patella before and immediately after exercise with the patient still sitting on the bicycle. The biopsy was frozen in liquid nitrogen at once and stored at −80°C for subsequent analyses. Enzyme activities (citrate synthase, 3-OH-acyl coenzyme A dehydrogenase and lactate dehydrogenase) and metabolic substrates and intermediates (adenosine triphosphate, creatine phosphate, glycogen, glucose, glucose-6-phosphate and lactate) were determined on homogenates of muscle tissue on the basis of principles described by Lowry and Passonneau[6] using a fluorimetric method of nicotinamide adenine dinucleotide–nicotinamide adenine dinucleotide phosphate coupled reactions. The protein content of muscle homogenate was analysed according to Lowry *et al.*[7]. Since the half-life of mitochondrial enzymes is at least 5 days[8], analysis of enzyme activity was performed as the mean of two samples (pre-exercise and postexercise), and

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expressed as μmol g^{-1} protein min^{-1}. Glycogen was analysed as glucose residues after the muscle sample had been hydrolysed with 1 M hydrochloric acid at 100°C for 2 h[9].

Statistics

Student's *t* test for paired and unpaired data was used to test statistical significance Linear regression (least squares) was used for assessment of association between two variables P values $<0{\cdot}05$ were considered significant

Ethics

All patients gave their consent to participate in the study The study protocol was approved by the Ethical Committee of Copenhagen Hospitals

Results

Fatigue

Fatigue (mean(s.e m.)) increased from 2·5(0·5) arbitrary units before operation to 4·6(0·5) arbitrary units on day 20 after surgery ($P<0{\cdot}001$).

Anthropometric measurements (Table 1)

Body-weight, triceps skinfold thickness and arm circumference decreased significantly from before to after surgery. There was a significant correlation between increase in fatigue and decrease in triceps skinfold thickness ($r=0{\cdot}72$, $P<0{\cdot}01$), but not between fatigue and arm muscle circumference ($r=0{\cdot}31$, $P>0{\cdot}1$) or between fatigue and arm circumference ($r=0{\cdot}03$, $P>0{\cdot}9$). There was no correlation between increase in fatigue and decrease in body-weight ($r=0{\cdot}34$, $P>0{\cdot}1$). One patient with loss of body-weight of 6·3 kg (7·4 per cent) had no increase in postoperative fatigue. The correlation between fatigue and weight loss without this patient was $r=0{\cdot}72$ ($P<0{\cdot}01$).

Table 1 *A comparison of anthropometric measurements taken before and after operation*

	Before operation	After operation
Body-weight (kg)	71 (4)	69 (4)*
Triceps skinfold thickness (mm)	20 (3)	19 (2)*
Arm circumference (cm)	29 (1)	28 (1)†
Arm muscle circumference (cm)	22 (1)	22 (1)

Values are mean(s e m); * $P<0{\cdot}01$, † $P<0{\cdot}02$, preoperative *versus* postoperative values

Heart rate (Figure 1)

Three minutes after the start of the postoperative exercise test, the heart rate was significantly higher than during the preoperative exercise test. There was a positive correlation between postoperative fatigue and increase in heart rate during exercise (postoperative minus preoperative values), being significant after 6 min of exercise ($r=0{\cdot}53$, $P<0{\cdot}05$). The correlation between the increase in postoperative fatigue and the difference between preoperative and postoperative heart rates during the last 6 min of exercise was also significant ($r=0{\cdot}41$, $P<0{\cdot}01$).

Muscle substrates and enzyme activities (Table 2)

During exercise before operation there was a slight decrease in adenosine triphosphate and a significant increase in creatine phosphate ($P<0{\cdot}05$), a decrease in glycogen ($P<0{\cdot}05$) and an increase in glucose, glucose-6-phosphate and lactate ($P<0{\cdot}05$).

After operation, at rest, the concentrations of glycogen and adenosine triphosphate were significantly higher ($P<0{\cdot}05$), and activities of citrate synthase and coenzyme A dehydrogenase were significantly lower ($P<0{\cdot}05$) than before operation.

After operation, after exercise, the concentrations of glucose

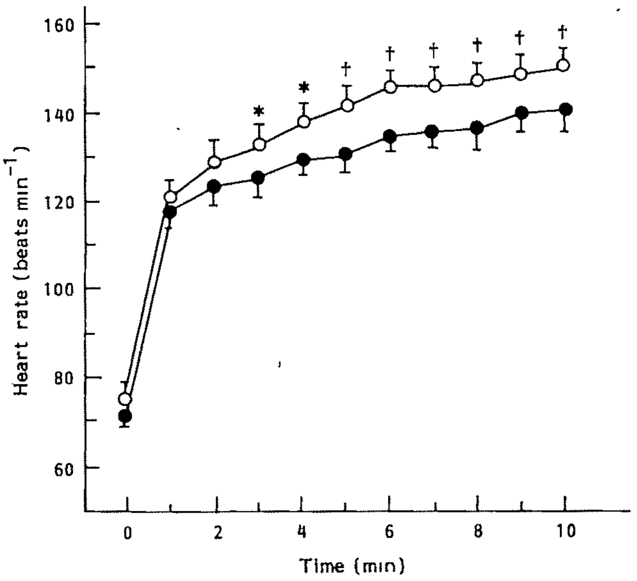

Figure 1 *Heart rate in 12 patients during bicycle exercise before surgery* (●) *and 20 days after surgery* (○). *Values are mean(s.e m.),* * $P<0{\cdot}02$, † $P<0{\cdot}05$

Table 2 *Biochemical parameters from muscle biopsies taken before and after exercise, before operation and postoperatively*

	Before operation		After operation	
	Before exercise	After exercise	Before exercise	After exercise
Glucose (mmol kg^{-1})	0·67 (0·06)	1·19 (0·11)*	0·79 (0·08)	1·58 (0·16)*†
Glucose-6-phosphate (mmol kg^{-1})	0·268 (0·03)	0·507 (0·04)*	0·234 (0·02)	0·565 (0·04)*
Glycogen (mmol kg^{-1})	72·4 (5·6)	50·6 (4·2)*	84·4 (4·2)†	55·6 (4·6)*
Lactate (mmol kg^{-1})	2·0 (0·4)	8·1 (1·3)*	2·4 (0·4)	10·5 (1·1)*†
Creatine phosphate (mmol kg^{-1})	16·5 (1·4)	10·8 (0·9)*	19·3 (1·0)	11·2 (1·2)*
Adenosine triphosphate (mmol kg^{-1})	4·7 (0·3)	4·4 (0·2)	5·5 (0·3)†	4·4 (0·2)
Lactate dehydrogenase (μmol g^{-1} min^{-1})	903 (70)		858 (59)	
Citrate synthase (μmol g^{-1} min^{-1})	36·6 (2·0)		31·3 (1·4)†	
3-OH-acyl coenzyme A dehydrogenase (μmol g^{-1} min^{-1})	45·4 (3·4)		40·7 (3·4)†	

Values are mean(s e.m), * values at rest *versus* during exercise ($P<0{\cdot}05$), † preoperative *versus* postoperative values ($P<0{\cdot}05$)

and lactate were significantly higher ($P<0{\cdot}05$) than before operation

When fatigue and muscle parameters were correlated, the only significant correlation was an inverse correlation ($r=-0{\cdot}65$, $P<0{\cdot}05$) between the increased fatigue after surgery and the decrease in muscle glycogen during the postoperative exercise test.

Discussion

This study confirms that uncomplicated abdominal surgery is followed by an increased feeling of fatigue[1-3,10], which correlates with an exaggerated cardiovascular response to exercise after operation[10]. A significant postoperative deterioration in nutritional status was found previously[1].

During preoperative exercise the changes found in muscle substrates and intermediates were in accordance with results described previously: a slight decrease in adenosine triphosphate and a significant increase in creatine phosphate ($P<0{\cdot}05$)[11-14], a decrease in glycogen ($P<0{\cdot}05$)[11,12,15-18] and an increase in glucose[18], glucose-6-phosphate ($P<0{\cdot}05$)[18,19] and lactate ($P<0{\cdot}05$)[11,12,18].

After operation, at rest, the concentrations of glycogen and adenosine triphosphate were significantly higher ($P<0{\cdot}05$), and those of citrate synthase and coenzyme A dehydrogenase were significantly lower ($P<0{\cdot}05$) than before operation.

After operation, after exercise, corresponding with the observed decreased postoperative capacity for oxidative phosphorylation as indicated in lower values of citrate synthase and coenzyme A dehydrogenase, glycogen and creatine phosphate showed a marked decrease in response to exercise (glycogen decreased by 21·8 mmol kg^{-1} before operation and by 28·8 mmol kg^{-1} after operation; creatine phosphate by 5·7 mmol kg^{-1} before operation and by 8·1 mmol kg^{-1} after operation). At the same time, the increase in glucose and lactate during exercise was significantly higher after operation

Important factors in the pathogenesis of postoperative fatigue and the postoperative changes found in muscles could be the surgical stress response; impaired nutritional intake in the convalescence period; and immobilization or lack of exercise in the first month after surgery

The influence of the surgical stress response on substrates and enzyme activities of skeletal muscle has been studied[20-22] during the first hour after cholecystectomy. lactate and citrate concentrations increased, while concentrations of glycogen, adenosine triphosphate and creatine phosphate were unchanged in the lateral vastus muscle[20]. Four days after total hip replacement a decrease in muscle adenosine triphosphate and creatine phosphate was observed[21] when the patients received only amino acids as postoperative nutrition, but not when they received glucose with or without amino acids. Small amounts of glucose may therefore be important for the maintenance of cellular energy levels. Seven to ten days after gastric or intestinal resection in six patients[22] there was a 56–80 per cent decrease in muscle glycogen concentration compared with the preoperative value. Four of these patients were also examined 18–21 days after surgery, and glycogen was found to have normalized in two patients 20 days after surgery. In the present study, the concentrations of muscle glycogen and adenosine triphosphate were significantly higher at rest after operation compared with preoperative resting values. Both sets of values, however, are within the normal range for resting muscle after an overnight fast.

Impaired nutritional intake may be a contributing factor in the present study to the significant loss of body-weight ranging from 0·5 to 7·4 per cent, but no significant correlation between postoperative fatigue and loss of body-weight was found, as had been previously demonstrated in a larger number of patients[1]. We neither found any correlation between changes in anthropometric measurements and changes in muscle substrates and enzyme activities after surgery, but it is emphasized that malnutrition was not present in these patients, in contrast with other studies on postoperative muscle biopsies. Thus, two studies[23,24] of undernourished surgical patients (weight loss greater than 10 per cent) found reduced activity of three key enzymes (fructose biphosphatase, phosphofructokinase and hexokinase) of glucose utilization in vastus lateralis ranging from 27 to 55 per cent of values in normally nourished control subjects. The authors concluded that the maximum glycolysis rate was reduced by up to 40 per cent in undernourished patients. Seven surgical patients with a weight loss of more than 7 per cent had low muscle glycogen, but values of energy-rich phosphates and lactate were within the normal range[25]. These changes in the biochemistry of skeletal muscle in undernourished patients may reduce the ability of such patients to utilize infused glucose loads and may contribute to weakness and fatigue after operation.

Immobilization and inactivity after surgery may be a concurrent factor to changes in muscle function after operation. Åström *et al.*[26] found decreased activities of citrate synthase in muscles from the thigh of healthy men after 7 days of immobilization, and other studies[27-29] found lower citrate synthase activity in untrained than in well trained subjects. In the present study the concentrations of the oxidative enzymes, citrate synthase and coenzyme A dehydrogenase, were significantly lower 20 days after surgery than before.

The importance of inactivity and training on muscle metabolite was studied in male subjects before and 4 weeks after bicycle training with only one leg[30]. Glycogen utilization was highest in the untrained leg, where the highest concentration of lactate was also found. Hurley *et al.*[27] found 41 per cent more muscle glycogen utilization during exercise before than after a 12-week programme of endurance exercise, and Sahlin and Henriksson[31] found a 30 per cent higher content of muscle lactate after contraction to fatigue in sedentary subjects compared with trained persons. Postoperative, postexercise glucose concentrations were significantly higher than preoperative postexercise values. Muscle glucose as assessed in the present study also reflects the extracellular glucose concentration, the extracelluar space constituting approximately 15 per cent of a muscle tissue sample. Since plasma glucose was unchanged during postoperative exercise[10], the larger increase in postoperative muscle glucose in response to exercise is probably due to a real difference rather than to a change in magnitude of the extracellular space.

The change in feeling of fatigue from before to after surgery correlated significantly with the increased working heart rate after operation (*Figure 1*), but not with any changes in muscle parameters either from before to after surgery or from before to after exercise. This correlation between fatigue and impaired cardiovascular adaptability to exercise may also be caused by a relative immobilization after operation.

In conclusion, our study confirms that uncomplicated surgery is followed by an increased feeling of fatigue, deterioration in nutritional status and decreased exercise capacity Our results confirm that a period of lack of exercise decreases exercise capacity and increases the heart rate response to a given exercise load. The changes demonstrated in muscle enzyme activities, substrate and metabolic intermediates also reflect the fact that immobilization leads to a decreased capacity of skeletal muscle for oxidative phosphorylation, and a higher degree of lactate formation. No relationship was found between postoperative fatigue and lactate or any other muscle parameter. Thus, our results suggest a therapeutic role for exercise, combined with sufficient dietary regimens, in the prophylactic treatment of postoperative fatigue.

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Immunodeficiency following splenectomy in the early postimmunization period

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Splenectomy is associated with an increased risk of serious infection with encapsulated micro-organisms in a small number of individuals. The immunological defects in this state are unclear. We have investigated in rabbits the effect of splenectomy, before and after primary immunization with a specific antigen (sheep erythrocytes) similar in structure to the pneumococcal capsular antigen, on the organ localization of antibody forming cells and the long-lived memory cells. Antibody forming cell and memory cell assays were performed at intervals up to day 270 after primary immunization. Antibody titres following secondary immunization were also measured. The results show that the major site of antibody forming cells is in the spleen following primary immunization of the untreated rabbit and that antibody forming cells subsequently migrate to the lymph nodes and thymus. On the other hand, in rabbits splenectomized before primary immunization the major site of the antibody forming cells is the peripheral lymph nodes. These rabbits also gave good secondary immune responses. However, splenectomy 40 days after primary immunization results in a poor secondary immune response, indicating that essentially all the antibody forming cells following primary immunization were localized in the spleen at the time of splenectomy.

Keywords: Splenectomy, immunodeficiency, immunization, antibody forming cells, memory cells

Patients who have undergone splenectomy are prone to overwhelming and often fatal sepsis. Although several organisms are involved, the encapsulated microorganisms, pneumococci and meningococci, pose the greatest threat[1,2]. Antibody production to invasive organisms following splenectomy is known to be impaired in some circumstances but the nature of this defect is unclear[3–5]. It is now generally accepted that the spleen is the organ in which antibody forming cells can first be detected in significant numbers following intravenous immunization[6]. Subsequently they may be found in other organs such as lymph nodes and thymus[6]. Memory cells are long-lived antibody forming cells which can exist in a dormant or inactive state for many months or years after which they may be stimulated by the original antigen to undergo transformation and proliferation into antibody forming cells. Memory cells are also found primarily in the spleen following immunization[6–9].

The purpose of this investigation was to localize both antibody forming cells and memory cells before and after splenectomy and to determine the effect of splenectomy on these cell types at various time intervals.

Materials and methods

The animals used were adult, immunologically mature, outbred, New Zealand White rabbits. Sheep red blood cells were used as the immunizing antigen; the cell membrane has a polysaccharide structure similar to the capsular antigen of the pneumococcus. The cells were washed several times in saline before use and 10^9 cells in saline were given intravenously.

The basic experimental design involved primary immunization of the animals. At intervals following immunization antibody forming cell and memory cell assays were done. Secondary immunization was then carried out and antibody titres measured before and 10 days after immunization.

The rabbits were divided into three groups. Group 1 ($n=40$) consisted of control animals, group 2 ($n=40$) had splenectomy performed 14 days before immunization, and group 3 ($n=15$) had splenectomy performed 40 days after immunization.

Animals in all three groups were injected intravenously with 10^9 sheep red blood cells in saline on day 1. At predetermined intervals from day 2 to day 270 after immunization, three rabbits from each group were killed by intravenous injection of 2·5 per cent sodium pentothal. The bone marrow and the lymphoid organs (spleen, thymus, lymph nodes, appendix, sacculus rotundus and Peyer's patches) were rapidly excised. Blood was obtained by cardiac puncture and drawn into heparinized syringes and diluted twofold with saline. The cells were expressed from the lymphoid organs. The mononuclear cells of the various organs and the blood were isolated by centrifugation through a Ficoll-Hypaque discontinuous density gradient. The cells were then washed in medium RPMI-1640 and assayed for antibody forming cells and memory cells.

The technique for identifying antibody forming cells was the plaque forming cell assay. The lymphoid cells were suspended with the antigen (sheep red blood cells) in the presence of complement in chambers between two glass slides for 2 h at 37°C. During this time, antibody secreted by the lymphoid cells diffused into the surrounding medium. The complement caused lysis of the sheep red blood cells which was apparent as a clear translucent halo surrounding the lymphoid cell (the plaque). The plaques were counted to estimate the number of antibody forming cells actively secreting antibodies.

Memory cells were assayed by the *in vitro* secondary immune response at 60, 120, 180 and 270 days after immunization. The mononuclear cells (4×10^6) were suspended in 4 ml of culture medium in sterile plastic tubes. Sheep red blood cells (4×10^6) were added and the cultures incubated at 37°C in 5 per cent carbon dioxide in air in the upright position. After incubation for 5 days, the cells were washed in medium RPMI-1640 and assayed for antibody forming cells using the plaque forming cell technique.

In addition, five animals in each group had circulating antibody titres determined immediately before and 10 days after *in vivo* secondary immunization on day 54 after primary immunization. The circulating antibody titres were determined using microtitre plates. Doubling dilutions of the antisera, heated to 56°C for 30 min to destroy complement, were made in 200 µl saline followed by the addition of 50 µl of a 1 per cent suspension of sheep red blood cells to each well. The plates were shaken and the agglutination patterns read 8–12 h

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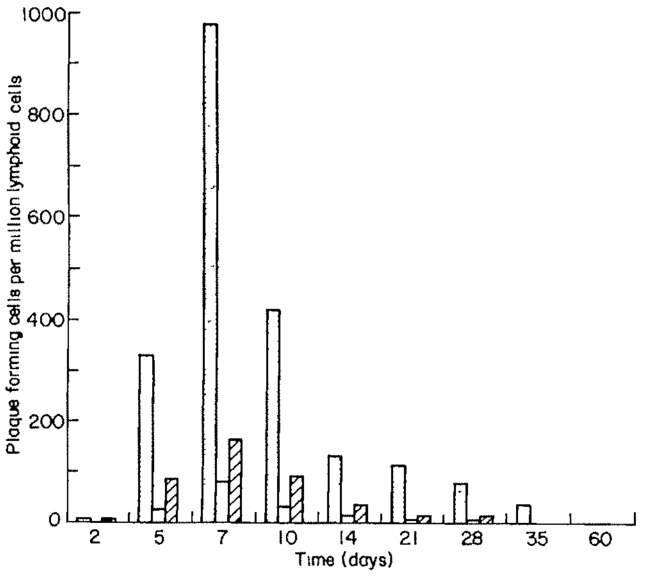

Figure 1 *Antibody forming cell assays of lymphoid cells after primary immunization.* □, *spleen,* □, *bone marrow,* ■, *blood*

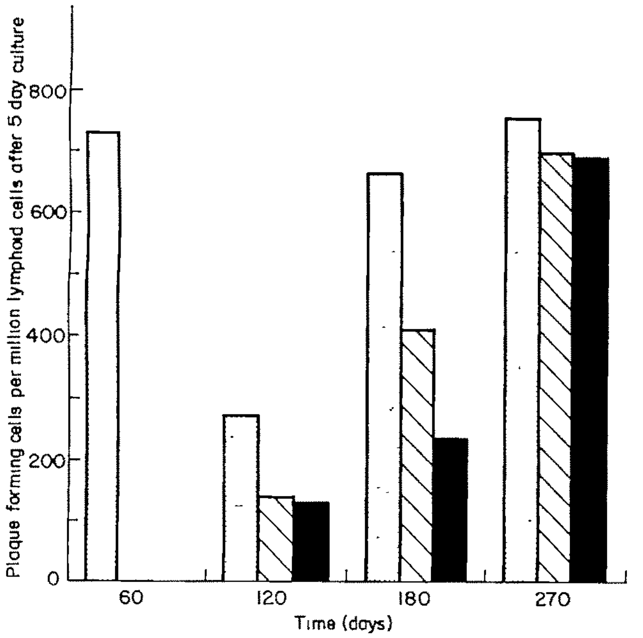

Figure 2 *Memory cell assays of lymphoid cells after primary immunization.* □, *spleen,* ■, *thymus,* ■, *lymph node*

later. The titre was the inverse of the maximum dilution which caused agglutination of the sheep red blood cells

Results

In the control group, after primary immunization with sheep red blood cells, antibody forming cells were detected first and in the greatest numbers in the spleen (*Figure 1*). Antibody forming cells were detected as early as 3 days after immunization and reached maximum numbers by day 7, after which they were reduced in number, none was detected in the spleen between days 60 and 270 after immunization. Antibody forming cells appeared in the circulation in much lower numbers by day 5, peaked at the same time as in the spleen, and disappeared by day 28. The number of antibody forming cells in the bone marrow was less and more transient than in the spleen and the circulation, though following the same time distribution curve Of significance, no antibody forming cells could be detected in any of the other lymphoid organs.

Memory cell assays were carried out in control animals at 60, 120, 180 and 270 days after immunization. Memory cells were found only in the spleen at 60 days but from 120 days they could also be found in the lymph nodes and the thymus (*Figure 2*)

The circulating antibody titres in the control rabbits rose markedly following secondary immunization compared with titres before secondary immunization (*Table 1*).

Splenectomy before immunization (group 2 rabbits) resulted in a primary immune response to sheep red blood cells which was localized to the lymph nodes; the antibody forming cells were detected between days 4 and 28 but maximally on day 7 (*Figure 3*). As in the control animals, antibody forming cells in the circulation and bone marrow paralleled the number of antibody forming cells in the lymph nodes but they were present in much lower numbers. Again, no antibody forming cells were detected in any other lymphoid organ. Memory cells were detected in signficant numbers in the lymph nodes by day 30 and in the thymus by day 60 (*Figure 4*).

Circulating antibody titres in these rabbits also rose markedly following secondary immunization, with a greater than tenfold increase in titres (*Table 1*).

Rabbits splenectomized 40 days after primary immunization (group 3 rabbits) were not able to produce antibody forming cells, as detected by the plaque forming cell assay, at any time up to day 270 after immunization. This might be expected since all antibody forming cells are sequestered in the spleen 40 days after immunization and would have been removed by splenectomy^{10}. Very poor memory cell responses were seen at 60, 180 and 270 days after primary immunization (*Figure 5*) This minimal antibody response may have been due to migration of a few memory cells to other lymphoid organs

Table 1 *Circulating antibody titres before and after secondary immunization*

	Circulating antibody titre					
	Group 1, controls		Group 2, splenectomy before immunization		Group 3, splenectomy after immunization	
Rabbit	Before	After	Before	After	Before	After
1	640	10240	160	1280	20	80
2	320	10240	160	2560	40	160
3	1280	20488	80	2560	320	320
4	1280	20480	80	5120	160	320
5	640	20480	80	5120	160	640

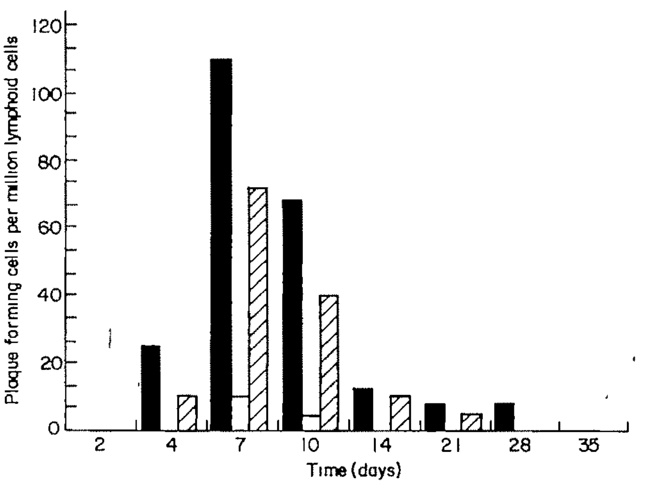

Figure 3 *Antibody forming cell assays of lymphoid cells after splenectomy before immunization* ■, *lymph node,* □, *bone marrow,* ■, *blood*

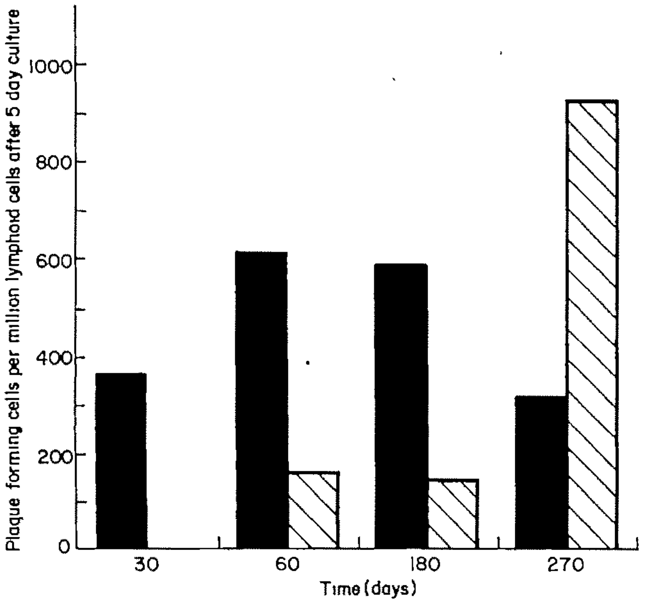

Figure 4 *Memory cell assays of lymphoid cells after splenectomy before immunization.* ■, *lymph node,* ■, *thymus*

before splenectomy. Animals in this group also demonstrated low circulating antibody titres following secondary immunization when compared with antibody titres before secondary immunization (*Table 1*).

Discussion

It is now well accepted in both adults and children that splenectomy may be followed by a small but definite risk of bacterial sepsis which is associated with a mortality rate of 60 per cent[11,12]. The pathophysiology of this postsplenectomy sepsis is not well understood. Several studies have shown delayed clearance of injected pneumococci from the circulation of splenectomized animals[13,14] This has been attributed to loss of the reticuloendothelial function of the spleen and may persist for up to 5 years[15]. Splenectomy has also been shown to increase mortality due to peritonitis from organisms that are normally cleared by the liver, indicating an effect of splenectomy other than its phagocytic function[16]. The cellular immune defects which may follow splenectomy are still unclear. Individuals subjected to splenectomy may form antibodies quite normally to antigens given subcutaneously but not respond well to antigen administered intravenously. This is most marked in children[17,18].

The present investigation confirmed previous findings that antibody forming cells are found first in the spleen following intravenous injection and that the spleen is the major organ involved in the immune response[6]. Antibody forming cells can also be found in much fewer numbers in the circulation, essentially paralleling their numbers in the spleen. However, they disappear from the circulation by day 35 and appear to be sequestered in the spleen for a further few weeks[10]. The small number of cells found in the bone marrow may be attributed to the conducive microenvironment which it presents to infiltrating cells. The other lymphoid organs do not appear to offer such an environment or cannot be stimulated by the antigen to produce antibody forming cells.

Memory cells could first be detected in the spleen on day 60 after primary immunization. By days 180 and 270 after immunization, memory cells were found not only in the spleen but also in the lymph nodes and thymus[6]. The other lymphoid tissues did not possess any memory cells. This would suggest that, following immunization, memory cells disseminate from the spleen to the lymph nodes and thymus. The possibility that memory cells could have originated in these organs can be discounted since these organs did not possess antibody forming cells at any time following immunization, as detected by the plaque forming cell assay, which is a necessary prerequisite for the subsequent appearance of memory cells.

Rabbits subjected to splenectomy before immunization are still able to mount a good antibody response, the antibody and memory cell response being mainly in the lymph nodes. They also show a significant increase in circulating antibody titres following secondary immunization.

Rabbits subjected to splenectomy 40 days after immunization, when all the antibody forming and memory cells are located in the spleen, appear capable of only a very limited immune response. Only a very few memory cells are found in the lymph nodes when assays are performed at 60, 180 and 270 days after primary immunization. In addition, circulating antibody titres show a minimal rise following secondary immunization.

Di Padova *et al.*[19] have reported that circulating B cells of normal individuals and individuals following splenectomy secrete equal quantities of IgG and IgM antibodies when cultured 7 days after immunization with polyvalent pneumococcal vaccine. However, only the B cells of normal subjects secreted IgG and IgM antibodies following culture with T cells and pokeweed mitogen 21 days after immunization. The lymph nodes may substitute for the spleen in the early phase following splenectomy but in the second phase the spleen was the main organ responsible for antibody production to polyclonal vaccine. This agrees with our findings that, once memory cells have migrated from the spleen, a satisfactory immune response is possible.

The antigen specific immunodeficient state may be attributed to the elimination by splenectomy of the majority of antibody forming cells and memory cells at a time when they are sequestered in the spleen (between days 35 and 120 after primary immunization). It is hypothesized that individuals who develop overwhelming postsplenectomy sepsis may have had a splenectomy at a stage in which all memory cells capable of recognizing an infecting encapsulated microorganism may have been present only in the spleen. They are therefore less capable of mounting a satisfactory immune response. The majority of individuals will probably have had a splenectomy at a time outside this relatively short 'spleen only' period of memory cell localization by which time memory cells will be found in the lymph nodes and thymus. They will then be capable of mounting a satisfactory immune response. This provides an explanation of why only a small number of individuals who have had a splenectomy succumb to this condition. Since it is

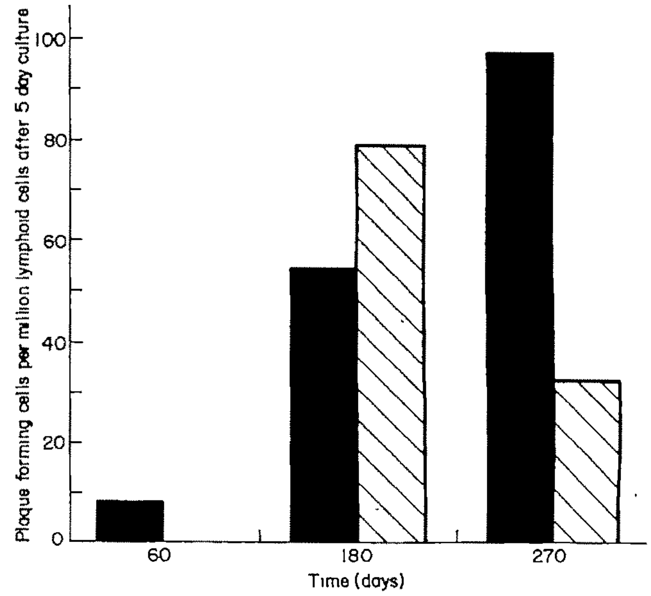

Figure 5 *Memory cell assays of lymphoid cells after splenectomy 40 days after immunization* ■, *lymph node;* ■, *thymus*

likely that the 'spleen only' period occurs primarily in childhood, soon after primary infection with an encapsulated microorganism, the postsplenectomy syndrome would be expected to be more prevalent in children than in adults following splenectomy. Whether or not delaying splenectomy until after immunization, following the dissemination of memory cells from the spleen to the thymus and lymph nodes, results in an immune response similar to that which occurs when splenectomy is performed before immunization is the subject of further investigation.

Overwhelming sepsis following splenectomy is probably multifactorial and the differing roles of decreased reticuloendothelial function and antibody synthesis remain to be further clarified. This study shows that antibody synthesis may be impaired but that this is dependent on the timing of splenectomy in relation to primary exposure to the infecting organism.

Acknowledgements

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Fine-wire localization and biopsy of non-palpable breast lesions

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We have undertaken fine-wire localization and biopsy of 130 impalpable breast lesions identified by mammography and considered suspicious of malignancy. Histologically 22 of these lesions were invasive carcinomas and 24 were in situ *carcinomas (35 per cent malignant). Twenty-nine per cent of the lesions were identified during the screening of asymptomatic women. In the remainder, the presenting symptoms bore no relation to the eventual histological diagnosis. Clusters of microcalcification were more often malignant than were abnormal soft-tissue masses. Malignancy in the absence of microcalcification was almost always invasive.*

Keywords: Breast carcinoma, mammographic localization, fine-wire localization, biopsy

Some breast screening programmes[1–5] have reported a significant reduction in the mortality from breast cancer in selected groups of women. Many of the detected lesions are apparent only on mammograms and such non-palpable lesions must be localized accurately to ensure adequate excision without unnecessary cosmetic defect.

Many methods of localization have been described but since its introduction in 1976 the use of the Frank needle® (William Cook (Europe) Ltd., UK) with a flexible hook-wire[6] has been particularly popular. We report our experience with this method in 130 biopsies from 126 patients.

Patients and methods

In an 8 year period, 130 biopsies were performed on 126 patients who presented in various ways (*Table 1*) Approximately one-third of all lesions were detected in asymptomatic women who attended screening clinics. Another third were detected in women with a breast lump who attended an outpatient clinic and were found on mammography to have a radiological lesion at a site remote from the palpable lump Most of the others (23·0 per cent) complained of painful breasts without a discrete lump and a few (10·3 per cent) complained of nipple discharge or itching. Two patients had lesions which were detected on mammographic assessment of a carcinoma of the opposite breast and seven patients on mammographic follow-up after previous mastectomy on the opposite side

All radiological localizations were done by, or under the immediate supervision of, two consultant radiologists Mediolateral and craniocaudal mammograms were used to judge the position of the lesion and the Frank needle was then inserted under local anaesthesia. A perforated grid was not used. Further mediolateral and craniocaudal mammograms were taken to check the accuracy of the localization. The wire was trimmed 4 cm above the skin surface and adhesive tape was attached like a flag to prevent migration of the end of the wire below the skin surface All X-rays and reports were sent to theatre with the patients. The operations were carried out under general anaesthesia through an incision designed to give a good cosmetic result. The fine wire was rarely palpable, therefore X-rays and the direction of the external portion of the wire were used as a guide to its location

A generous block of tissue around the tip of the wire was excised. The specimen was sent unfixed for X-ray and the patient kept anaesthetized with the wound unsutured until radiological confirmation of removal The specimen, with its contained wire, was then placed in formalin and sent to the pathology laboratory where it was sectioned, pinned out and X-rayed The X-rays of the specimen ensured that adequate sections were taken from the suspicious area and from the surrounding tissue. When the pathology report was available, X-rays and slides were reviewed in conference by all the clinicians and a decision made regarding further management.

Results

Mode of presentation

The mode of presentation and positive biopsy rates are shown in *Table 1*. The incidence of malignancy was not related to the mode of presentation and the malignancy rate was similar in symptomatic and asymptomatic women.

Technical difficulties and errors

Of the 130 localizations, 20 were classed as 'technically difficult'; usually more than two wires were required for accurate localization or, in a few cases, the radiologist had difficulty inserting wires into dense glandular breasts.

Surgical difficulties were few. In one patient the wire in the axillary tail was trimmed close to the skin, slipped below the surface of the breast during skin preparation and could not be located at operation This patient required two wires for localization and the remaining wire guided excision. The 'lost' wire subsequently extruded spontaneously.

In three patients the radiological lesion was not seen in the specimen radiograph and wider excision demonstrated malignancy in the second piece of tissue in each.

In two patients the lesion was not present on specimen radiography and the surgeon was unaware of this. In one a benign lesion was successfully excised at a second operation. The second patient continues under careful clinical and mammographic review.

In five patients the specimen was not sent for X-ray as a definite mass was found at the tip of the needle. Two were cysts, two were hyalinized fibroadenomas and one an invasive lobular carcinoma.

Histopathology

The principal histological diagnoses are shown in *Table 2*. Of the 67 lesions designated fibrocystic disease, four had foci of atypical ductal hyperplasia and two had foci of atypical lobular hyperplasia. The rate of malignancy was 35 per cent, with 48 per cent of the carcinomas being invasive and 52 per cent *in situ*. Thirty-seven (80 per cent) of the malignant lesions (14 invasive

Table 1 *Presentation*

	All patients ($n = 126$) Number (%)	Cancers only ($n = 46$) Number (% of patients of each group)
Screening of asymptomatic women	36 (28·6)	13 (36)
Lump, remote from mammographic lesion	39 (31·0)	10 (26)
Pain	29 (23·0)	11 (38)
Nipple symptoms	13 (10·3)	7 (54)
Previous/current carcinoma	9 (7·1)	5 (56)

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Table 2 *Histopathology of 130 lesions in 126 patients*

Malignant	
Invasive ductal carcinoma	17
Invasive lobular carcinoma	3
Tubular carcinoma	2
In situ ductal carcinoma	21
In situ lobular carcinoma	3
Total	46
Benign	
Fibrocystic disease	67
Fibroadenoma	13
Duct ectasia	2
Scar tissue (postsurgical)	1
Atrophic lobules	1
Total	84

Table 3 *Mammographic features and pathological diagnosis*

	All lesions ($n=130$) Number (%)	Malignancies ($n=46$) Number of invasive + *in situ* (% of patients in each group)
Microcalcification	83 (63·9)	12 + 21 (40)
Irregular opacity or architectural disturbance	35 (26·9)	8 + 1 (26)
Opacity plus microcalcification	12 (9·2)	2 + 2 (33)

and 23 *in situ*) had shown microcalcification on mammography. Of these 34 were invasive or *in situ* ductal carcinomas and the other three were *in situ* lobular carcinomas In the latter three the microcalcification was all sited in an area of benign disease (predominantly sclerosing adenosis) adjacent to the malignant focus. In the ductal lesions microcalcification was entirely within the malignant focus in 26 specimens In only one specimen was the calcification entirely outside the malignant focus.

Treatment

Twenty-three (50 per cent) of the 46 patients with malignancy underwent mastectomy. The proportion was similar for invasive (10 of 22) and *in situ* lesions (13 of 24). Determining factors included the presence of multiple foci of tumour, the proximity of the lesion to the nipple and the preference of the patient. Patients who were not treated by mastectomy underwent wide local excision and in many the original biopsy excision was considered sufficiently wide. If carcinomas were invasive, patients received radical radiotherapy to the area of excision.

Axillary node sampling was performed on those patients who underwent mastectomy Two patients had positive axillary nodes and both had had invasive ductal carcinoma, a node-positive rate of 20 per cent for patients with invasive carcinoma No patient undergoing mastectomy for *in situ* carcinoma had positive axillary nodes.

Mammographic features and pathological diagnosis

The relationship between mammographic features and malignancy rate is shown in *Table 3* The incidence of malignancy was greater in those lesions associated with microcalcification than in those without. If an opacity without microcalcification proved to be malignant it was almost always invasive. Only one of 35 such lesions had no identifiable invasion.

Radiologist's assessment and pathological diagnosis

Table 4 shows the relationship between the radiologist's assessment of the likelihood of malignancy and the pathological diagnosis. The designations 'radiologically benign' and 'radiologically malignant' were applied only to unequivocal reports. Nine lesions originally reported as radiologically benign were biopsied for patient reassurance. In one patient a rounded opacity was reported as benign but biopsy was advised because the patient was aged 61 years. This was the single carcinoma in the 'radiologically benign' group.

We are unable to report our false-negative rate, i.e. the proportion of *all* lesions reported benign that will subsequently prove to be malignant.

Discussion

The radiological criteria for malignancy are well known[7,8] but interpretation is subjective. Biopsy rates vary from 7·5 to 91 per 1000 women screened[7]. Reports of positive biopsy rates range from 10 per cent to 50 per cent[9,10] and more than half are less than 30 per cent[11]. The positive biopsy rate does not necessarily improve with experience For example, in the largest reported series it was 32 per cent after the first 180 cases[12] and 23 per cent after 500 cases[13].

Our positive biopsy rate was 35 per cent and, of the 46 malignant lesions detected, 22 (48 per cent) were invasive carcinomas. This proportion of invasive carcinomas is lower than the 55 per cent reported from Edinburgh[14] and Birmingham[15] and very much lower than the 75 per cent reported from Liverpool[7] and Boston[13].

It is difficult to compare the mode of presentation (*Table 1*) with other reports because this information is not generally given. The similar positive biopsy rates in symptomatic and asymptomatic patients suggests that the mammographic abnormalities detected were not related to the presenting symptoms

Immediate specimen radiography, with the patient still anaesthetized, is important and we advocate early multidisciplinary review of all cases to detect errors in communication that can occur at the time of biopsy

In those with lobular *in situ* carcinoma the microcalcification was always situated in an area of benign disease (predominantly sclerosing adenosis) adjacent to the malignant focus Others have noted similar findings and comment upon their implications for biopsy technique[15].

Half our patients with malignant lesions underwent mastectomy and only two had positive axillary nodes. This is a similar rate to groups in Birmingham[15] (20 per cent) and Edinburgh[14] (18 per cent), where axillary node sampling was undertaken on all patients with malignant lesions.

The relationship between pathological diagnosis and mammographic features is similar to that found in Manchester, Edinburgh[14] and Birmingham[15]. Microcalcification is more likely to be associated with *in situ* than with invasive malignancy, whereas malignancy associated with an opacity is usually invasive, especially if there is no microcalcification.

Comparison between radiological assessment and final histological diagnosis suggests that the decision to biopsy should not be made solely on radiological grounds. The single cancer considered radiologically benign was biopsied on grounds of age alone We advocate a generous biopsy, compatible with a good cosmetic result, because of the technical difficulty of identifying the tip of the guide wire at operation and because microcalcification may be adjacent to the malignant focus

Mammography can only identify those lesions suspicious of malignancy and indicates a need to undertake biopsy Improved radiological techniques (such as image magnification and stereotactic localization) and the establishment of quality

Table 4 *Radiologist's assessment and pathological diagnosis*

	All lesions ($n=130$) Number (%)	Malignancies ($n=46$) Number (% of lesions in each group)
Radiologically benign	9 (6·9)	1 (11)
Possibly malignant	99 (76·2)	31 (31)
Radiologically malignant	22 (16·9)	14 (64)

assurance protocols will enable more centres to achieve the high specificity reported from units such as Guildford[16] without any loss of sensitivity.

One-third of our patients were referred by screening clinics for asymptomatic women. Implementation of the Forrest report[17] will make this technique available throughout the UK.

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Short note

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Assessment of surgical excision during breast conservation surgery by intraoperative two-dimensional specimen radiology

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Early results in prospective trials suggest that women with small breast carcinomas treated by wide local excision and radiotherapy fare no worse than those treated by mastectomy[1,2]. If conservation surgery is being undertaken the specimen margins must be clear of all invasive and *in situ* carcinoma. In an attempt to achieve a good cosmetic result, particularly if the breast is small or the carcinoma large, the surgeon may occasionally encroach close to the tumour. If excision is incomplete a second operation to excise the bed of the carcinoma or to perform a mastectomy is required.

Fisher *et al.*[1] assessed the specimen margin by intraoperative frozen section and the 10 per cent of patients in whom the carcinoma extended to a margin underwent immediate mastectomy. Intraoperative cytology has also been evaluated[3]. Both techniques require considerable pathological expertise and close cooperation with the surgeon Such facilities will not be available outside specialist centres and a simple intraoperative aid to assist the surgeon would be valuable.

In a recent study specimen radiology showed a high degree of resolution between carcinomas and the surrounding normal tissue[4]. If normal tissue could be shown to surround the carcinoma adequate excision might be predicted. This present study evaluates two-dimensional specimen radiology as an aid to determining the completeness of tumour excision during breast conservation surgery.

Patients and methods

Women undergoing wide local excision for breast carcinomas <4 cm diameter were studied. An elliptical skin incision incorporating the site of the previous needle aspiration was made and the dissection deepened to the fascia overlying the pectoralis muscle so that the carcinoma could be removed with an estimated 1 cm of surrounding tissue. The medial, superior and deep borders of the specimen were marked with one, two and three metal clips respectively, and it was then sewn into a radiolucent plastic box such that its orientation would remain constant (*Figure 1*) The surgeons changed their gloves and the operation was completed The specimen was X-rayed in two planes at right angles (Faxitron, Hewlett Packard, Palo Alto, California, USA, Model 43805N) at 25–35 kV for 60–120 s depending on specimen size (*Figure 2*). A screen pack was not used

The unfixed oriented specimen and the specimen radiograph were compared by the pathologist (J J.G.). The specimen was sliced with a dermatome blade into parallel, 4 mm, slices and the resection margins of blocks chosen for histological examination were marked with Indian ink Blocks were selected to show the relationship between the carcinoma and resection margins as accurately as possible

Results

Forty-six women were studied (*Figure 3*). In five radiographs (11 per cent) the carcinoma was not visualized because the bulk of the excised specimen prevented adequate X-ray penetration. In 17 radiographs (37 per cent) the margin of the carcinoma could be clearly seen only in the lateral view.

The carcinoma extended to the resection margin in nine specimens but only in one was this predicted by the specimen

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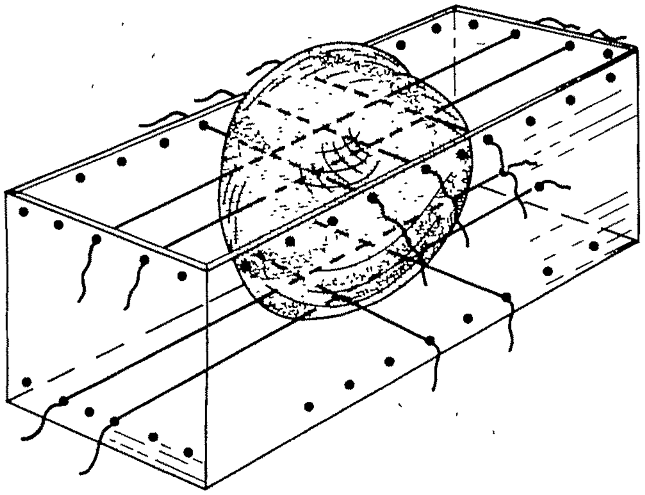

Figure 1 *Diagrammatic representation of the specimen sewn into the radiolucent box*

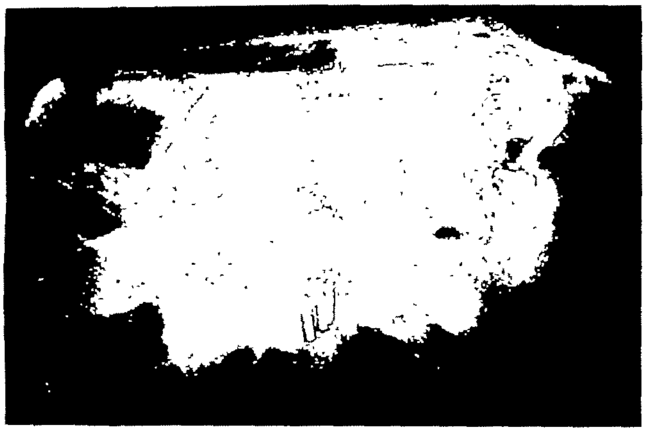

Figure 2 *A specimen radiograph in two views at right angles showing the invasive carcinoma (dense tissue) surrounded by the radiolucent normal tissue*

radiograph. Conversely, the carcinoma did not extend to the specimen margin in 32 specimens but in eight of these (25 per cent) the specimen radiograph was interpreted as showing involvement of the specimen margin. The specificity (ability of specimen radiology to detect a margin free of carcinoma) and sensitivity (ability of specimen radiology to detect a carcinoma involving the margin) of specimen radiology were 75 per cent and 11 per cent respectively.

Discussion

In this study specimen radiology was able to predict extension of a carcinoma to the specimen margin on only one of the nine occasions that it occurred. It was of no practical value as an intraoperative aid to the surgeon In many women the quality of the specimen radiograph precluded assessment in at least one plane, and even when the quality was satisfactory in both planes the predictive value was low.

The value of two-dimensional specimen radiology as attempted in this study must not be confused with the use of specimen radiology during localization biopsy for non-palpable mammographic abnormalities. In this study the ability of specimen radiology to determine the adequacy of a known carcinoma was being assessed, whereas specimen radiology of localization biopsies, which is mandatory, is performed to determine that the mammographic abnormality has been retrieved[5].

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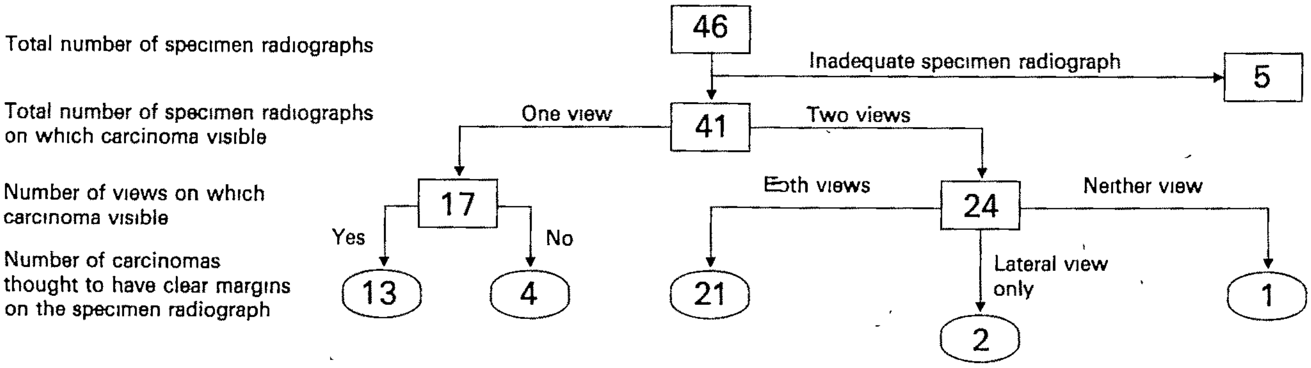
Total number of specimen radiographs
Total number of specimen radiographs on which carcinoma visible
Number of views on which carcinoma visible
Number of carcinomas thought to have clear margins on the specimen radiograph
46
Inadequate specimen radiograph
5
One view
41
Two views
17
Yes
No
13
4
Both views
24
Neither view
21
Lateral view only
2
1

Figure 3 *Correlation of specimen radiography and histological outcome*

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Measurement of serum thyroglobulin is of value in detecting tumour recurrence following treatment of differentiated thyroid carcinoma by lobectomy

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Serum thyroglobulin was measured in 243 samples from 84 patients (20 men and 64 women, with a mean age of 48·9(14) years) with differentiated thyroid carcinoma treated by lobectomy, and in 58 patients treated by total thyroidectomy. Both groups were given thyroxine to suppress thyroid stimulating hormone (TSH). Three patients in the lobectomy group and eight in the thyroidectomy group had evidence of tumour recurrence. Serum thyroglobulin concentration was elevated in the presence of known recurrent tumour ($P<0{\cdot}001$) *irrespective of the type of operation, and in its absence tended to be higher in the lobectomy than in the thyroidectomy group (median 4 μg/l* versus *2 μg/l,* $P<0{\cdot}05$)*. Serum thyroglobulin levels of less than 10 μg/l could confirm the absence of otherwise known tumour recurrence in both groups with a specificity of 100 per cent, and sensitivities of 80 per cent and 86 per cent in the lobectomy and thyroidectomy groups respectively. Exclusion of samples liable to spurious elevation of thyroglobulin improved the sensitivity in the lobectomy group to 92 per cent. Despite the presence of residual thyroid tissue, measurement of serum thyroglobulin can exclude the presence of significant metastases in most patients following lobectomy for thyroid carcinoma.*

Keywords: Thyroglobulin, thyroid carcinoma, thyroid lobectomy

It is now known that measurement of serum thyroglobulin is useful in the detection of recurrent disease after the treatment of differentiated thyroid carcinoma by total thyroidectomy, with or without subsequent ablative radioiodine therapy[1,2]. The discriminatory value of thyroglobulin measurement is greatest in patients taking thyroxine to suppress pituitary thyrotrophin (TSH) secretion[3] It seems that, in the majority of cases, serial measurements of serum thyroglobulin obviate the need for repeated whole body radioiodine scans after withdrawal of thyroid hormone therapy. In many centres the usual therapy for thyroid carcinoma remains total thyroidectomy However in Aberdeen, during the past 20 years, lobectomy with isthmusectomy has been the most common operation for differentiated thyroid carcinoma apparently limited to one lobe. After operation patients are given long-term suppressive doses of thyroxine, but do not normally receive radioiodine. As functional normal thyroid tissue remains in these patients, radioiodine scans are of limited value in screening for recurrent disease. The purpose of this study was to assess the value of serum thyroglobulin measurement.

Patients and methods

Eighty-four patients (20 men and 64 women) who had been treated for histologically proven, invasive, differentiated thyroid carcinoma by conservative surgery, and subsequently maintained on suppressive thyroxine, were studied. In three patients the tumour had been in the isthmus, and this part of the gland alone had been resected. In one patient, in whom local recurrence later developed, the primary tumour was in a thyroglossal cyst Lobectomy with isthmusectomy on the affected side had been performed in the remaining 80 patients The mean(s d.) age was 48 9(14) years (range 16–82 years), and the median duration of follow-up from operation to the time of analysis was 51 months (range 4–232 months). By the time of analysis three patients had developed evidence of recurrent tumour. This was clinically obvious in two, being disseminated in one and treated by local excision in the other The third patient, who complained of back pain, was treated for presumed recurrence with high dose radioiodine (3700 MBq) in a two-stage procedure, metastatic tumour was later confirmed by abnormal bony uptake of radioiodine on a whole body scan performed 1 week after the second dose Patients who had had a total thyroidectomy or who had received radioiodine ablation immediately after operation were excluded.

At each outpatient review the patients were examined for clinical evidence of tumour recurrence. A 10 ml sample of venous blood was obtained, allowed to clot at room temperature, separated and the serum stored at −20°C for subsequent assay for thyroglobulin, TSH and thyroglobulin autoantibodies (TgAb) Serum thyroglobulin was measured by an in-house radioimmunoassay, based on the method of Black *et al*[3], with a sensitivity of 1 μg/l and intra- and interassay coefficients of variation of 8 per cent and 16 per cent respectively Thyrotrophin was assayed by a high sensitivity two site commercial kit (Amerwell® or Amerlite®, Amersham International, Amersham, UK), in each case the limit of sensitivity being 0 1 milliunits/l. An in-house enzyme-linked immunosorbent assay method, based on that of Chan *et al.*[4] was used for the measurement of TgAb. The histological report on the thyroidectomy specimen from each patient was examined and any evidence of coexistent autoimmune thyroiditis noted

For comparison a group of 58 patients with differentiated thyroid carcinoma treated by total thyroidectomy and radioiodine ablation was also studied. Although these patients had been treated in London, their serum samples were analysed in Aberdeen using the same assays as described. They were also on suppressive thyroxine, and the two groups were of a similar age and sex distribution. The group treated by total thyroidectomy had been screened regularly for recurrent disease by whole body radioiodine scans after withdrawal of thyroxine In eight

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Table 1 *Serum thyroglobulin levels in all samples according to known recurrence and type of operation*

	No recurrence (µg/l)	Recurrence (µg/l)	*P*
Lobectomy	4(<1–99) (*n*=233)	45(16–>256) (*n*=10)	*P*<0·001
Total thyroidectomy	2(<1–115) (*n*=50)	47(18–>256) (*n*=8)	*P*<0·001
P	*P*<0·05	n.s.	

Values are median(range). Statistical analysis by non-parametric tests, n.s., not significant

of these patients there was clinical, radiographic or radionuclide scan evidence of recurrence at the time of sampling.

Serum thyroglobulin data were analysed on an individual sample basis according to the known presence, or otherwise, of recurrent disease at the time that the sample was taken. Statistical analysis was by non-parametric tests throughout

Results

Between December 1985 and November 1988 a total of 243 samples were obtained from the 84 patients treated by conservative surgery, including ten samples from the three patients with known tumour recurrence at the time of sampling. There were more patients with known recurrent disease among those treated by total thyroidectomy, 8 of 58 *versus* 3 of 84 ($\chi^2=4{\cdot}99$, $P<0{\cdot}05$), but different methods were used to detect recurrence in the two groups. In both groups median serum thyroglobulin was significantly higher in samples from patients with known recurrence compared with the remainder (*Table 1*). In patients without known recurrence, median serum thyroglobulin was higher in samples from patients treated by lobectomy when compared with total thyroidectomy (*Table 1*), but the overall pattern of distribution was similar, there being some unexplained high levels in both groups (*Figure 1*).

In all samples from patients with known recurrent disease thyroglobulin was greater than 10 µg/l. Using this value as a cut-off point, otherwise proven tumour recurrence could be detected by a serum thyroglobulin of greater than 10 µg/l with a sensitivity of 100 per cent in patients treated by either lobectomy or total thyroidectomy. In samples from patients without evidence of recurrent tumour, and treated by lobectomy alone, serum thyroglobulin was less than or equal to 10 µg/l in 186 (95th centile 28 µg/l), higher levels being found in 47 samples. The apparent specificity for detection of tumour recurrence was only 17·5 per cent, but absence of otherwise detectable recurrence could be confirmed with a specificity of 100 per cent and sensitivity of 80 per cent.

Thyroglobulin is released from normal thyroid in response to TSH stimulation[5], and serum levels may be elevated in autoimmune thyroiditis[6]. In addition high levels would be anticipated soon after operation, and in serum with high titres of TgAb, which can interfere with the thyroglobulin assay From the patients without known recurrence, treated by conservative surgery, there were 47 samples in which thyroglobulin levels were greater than 10 µg/l. TSH was detectable in 11 (median 1·2 milliunits/l, range 0·11–6·2 milliunits/l), the TgAb titre was greater than 1/20 in 13 (median 1/80, range 1/40–1/5120), the interval after surgery was less than 1 month in one sample, and 12 were from patients with histological evidence of autoimmune thyroiditis. More than one of these factors was applicable in nine of these samples In the 89 samples from patients treated by conservative surgery and without known recurrence, fulfilling one or more of these criteria, serum thyroglobulin was significantly higher than in the remaining 144 (median 7 µg/l *versus* 3 µg/l, $P<0{\cdot}001$), suggesting that these factors may account for the elevated measured serum thyroglobulin levels in at least some samples. When such samples were excluded there remained 19 samples from 15 patients treated by conservative surgery and without known recurrence, in which serum thyroglobulin (median 18 µg/l, range 11–55 µg/l) was greater than 10 µg/l for no apparent reason. Two of these samples (40 and 48 µg/l thyroglobulin) were from one of the three patients treated by isthmusectomy. In the two samples from the second patient treated in this way, who also had

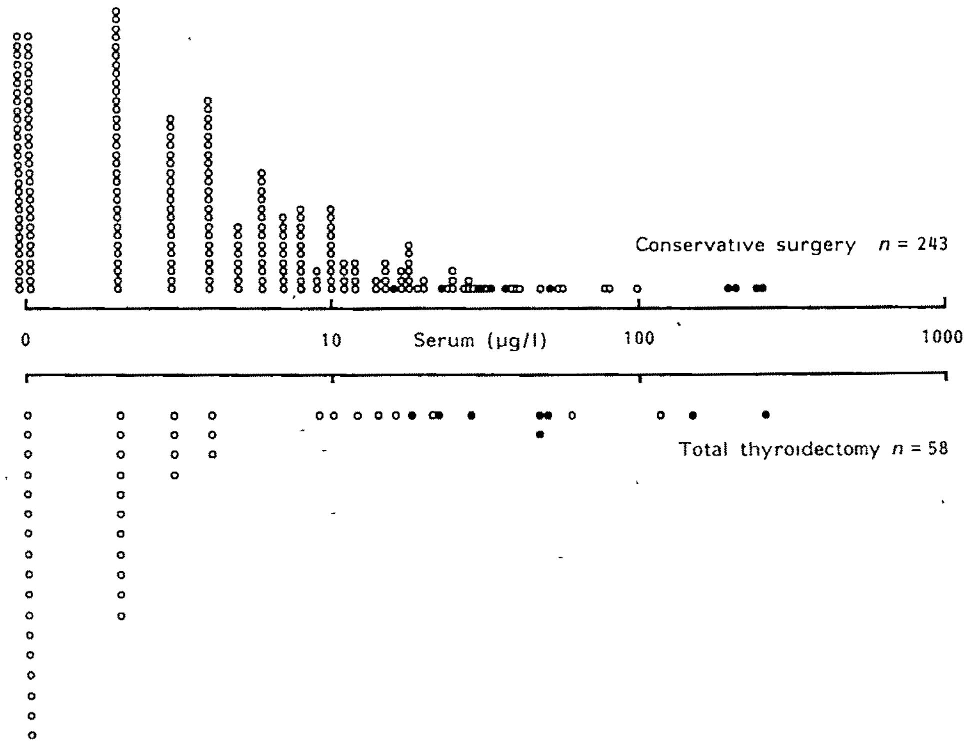

Figure 1 *Distribution of serum thyroglobulin in all samples according to type of surgery.* ●, *presence and* ○, *absence of known recurrent tumour*

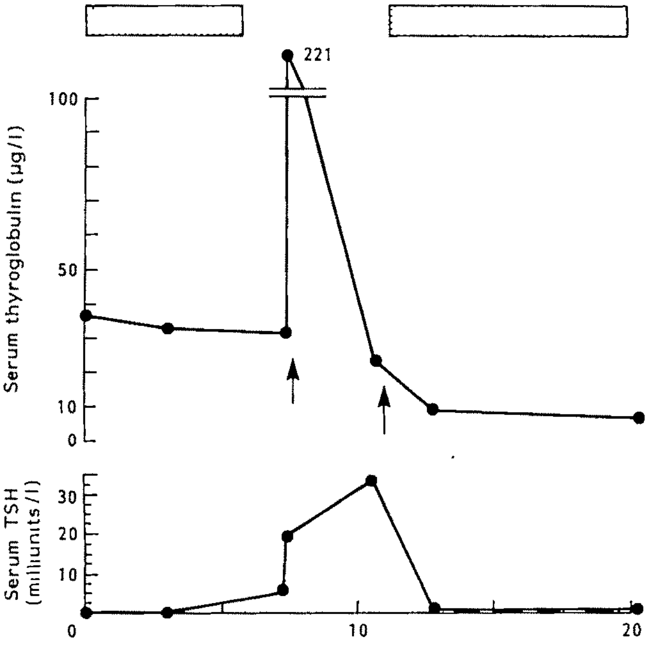

Figure 2 *Serum thyroglobulin and thyroid stimulating hormone concentrations in a patient initially treated by thyroid lobectomy, and who had retrospectively proven bony metastases, before, during and after two-stage radioiodine treatment (3700 MBq, indicated by the vertical arrows).* □, *periods of treatment with thyroxine 200 µg daily*

moderate titres of TgAbs, serum thyroglobulin was also elevated (23 and 28 µg/l), but was low, albeit detectable (6 µg/l), in the third patient.

Discussion

In the patients treated by conservative surgery the incidence of known tumour recurrence, as measured by the relatively crude method of clinical examination, was low and this in itself would tend to contribute to the high incidence of apparently false positive results when serum thyroglobulin was used to screen for recurrence. The overall apparent false positive rate was 82 per cent reducing to 66 per cent after exclusion of samples with possible other causes for a high serum thyroglobulin level, and compares with a rate of 46 per cent in the patients treated by total thyroidectomy. In the majority of patients there was no clinical evidence of recurrent tumour, and in these there was good concordance between absence of known recurrent disease and serum thyroglobulin levels of less than 10 µg/l. Overall, in patients treated by conservative surgery this was 80 per cent, improving to 92 per cent when samples with other potential causes for an elevation in serum thyroglobulin were excluded, and 86 per cent in patients treated by total thyroidectomy

Our results suggest that measurement of serum thyroglobulin is useful in excluding clinically significant recurrent tumour in patients treated for differentiated thyroid carcinoma by thyroid lobectomy and subsequent thyroxine, despite residual potentially functioning normal thyroid tissue, and support the findings of Schlumberger *et al.*[7] and De Vathaire *et al.*[8], although in the patients studied by Schlumberger discrimination was limited by failure to fully suppress serum TSH. The high rate of apparently false positive results renders the test less useful in determining recurrence, but it does allow identification of a relatively small group of patients in whom close surveillance and a high index of suspicion is justified. The exact causes of the false positive results are unknown, but it is likely that some of the patients with elevated serum thyroglobulin levels harbour occult tumour yet to declare itself clinically. This has often been found to be the case after long-term follow-up of similar patients[9] In assessing the significance of an elevated serum thyroglobulin after lobectomy, it is important to ascertain that there is adequate suppression of serum TSH, and to consider the possibility of coexistent autoimmune thyroiditis, a situation in which thyroglobulin tends to be constantly elevated over a period of time Thyroglobulin autoantibodies may cause a spurious elevation of measured thyroglobulin, but this occurs only at high titres in our thyroglobulin assay which can detect both free thyroglobulin and thyroglobulin bound to autoantibodies, both of which originate from the thyroid. Lower titres of TgAb may be significant in the context of false positive results, by acting as markers for underlying autoimmune thyroiditis. Finally, although we observed only small numbers, it would appear that serum thyroglobulin levels should be interpreted with caution in patients in whom both thyroid lobes remain.

In practical terms we would recommend an annual measurement of serum thyroglobulin and TSH after lobectomy for differentiated thyroid carcinoma. No action is required when the serum thyroglobulin is less than 10 µg/l In patients with higher levels, adequate suppression of serum TSH to below the limit of sensitivity of a high sensitivity assay should be ascertained, the possibility of other interfering factors considered, and further samples measured after a few months. It is now our policy to treat patients with progressively rising concentrations of serum thyroglobulin, and therefore presumed occult recurrence, with ablative radioiodine in a two-stage procedure. A whole body scintiscan after the second dose of radioiodine may provide retrospective confirmation of the occurrence of metastases. *Figure 2* shows an example of serum thyroglobulin levels before, during and after two-stage ablative radioiodine therapy in one such patient. Abnormal bony uptake of radioiodine, indicative of metastases, was demonstrated after the second dose of radioiodine.

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Thallium isotope scintigraphy and ultrasonography: comparative studies of localization techniques in primary hyperparathyroidism

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Controversy exists about whether preoperative localization procedures are indicated in patients with primary hyperparathyroidism before first neck exploration. Currently, thallium subtraction scintigraphy and ultrasonography are the techniques used most frequently. This paper examines prospectively the accuracy and value of these techniques in a group of 71 patients with primary hyperparathyroidism. When considering all glands, thallium scanning produced a sensitivity of 46·6 per cent with a specificity of 91·5 per cent, compared with a sensitivity of only 21·4 per cent and specificity of 94·5 per cent for ultrasonography. Accuracy rates, for all glands, were 80 per cent and 75·7 per cent respectively. Both localization procedures were consistently ineffective in localizing adenomas weighing less than 500 mg, over 80 per cent of which went undetected by both scanning modalities. While both scans produced satisfactory results in localizing adenomas weighing more than 1 g, these adenomas should not represent a challenge to an experienced endocrine surgeon and, therefore, neither localization is recommended before first neck exploration.

Keywords: Hyperparathyroidism, scintigraphy, ultrasonography, localization

Surgical treatment of primary hyperparathyroidism without the aid of preoperative localization studies can achieve excellent results with a return to clinical and biochemical normality in over 90 per cent of patients[1]. The use of localizing techniques, however, might allow more successful neck exploration with reduced morbidity (shorter operating time with or without unilateral neck explorations). Oesophageal fluoroscopy[2], cineradiography[3] and thermography[4], with more invasive procedures such as arteriography and selective venous sampling, have been employed.

Subtraction scintiscanning, using ^{201}thallium[5], and ultrasonography[6] are non-invasive procedures but it remains unclear which of these investigations is preferable and whether any procedure is sufficiently accurate to influence surgical strategy.

This study, therefore, examined the accuracy of thallium scintiscanning and ultrasonography to assess their role in the surgical management of patients with primary hyperparathyroidism.

Patients and methods

From 21 November 1983 to 29 January 1988, a total of 71 patients underwent bilateral cervical parathyroid exploration, following a diagnosis of primary hyperparathyroidism. All the operations were performed by the same surgeon and each patient had a preoperative thallium scintiscan and a cervical ultrasound examination in an attempt to localize abnormal parathyroid tissue.

In the case of thallium scintigraphy, each procedure was conducted by the same operator (B.C.), while for ultrasonography, seven scans were performed by two operators and 64 by the chief operator (P.G.R.). In every case these procedures were performed within 10 days of each other and the information derived from one was not available to the operator performing the other.

Surgery was performed within 9 weeks of these scans and, although the results of the scans were known to the surgeon, they did not influence the decision for operative intervention. Operative strategy was to explore both sides of the neck attempting to visualize all four parathyroid glands. Operative findings were carefully recorded and compared with the results of the preoperative localization procedures. All abnormal parathyroid tissue was weighed on a microbalance and was sent to the department of histopathology with at least one other biopsy specimen of a macroscopically normal parathyroid. The specimens were examined by peroperative frozen section and later by paraffin section.

A more aggressive surgical strategy with more biopsies results in a higher incidence of postoperative hypocalcaemia[7]. If a gland was not visualized it was assumed to be normal if biochemical normality was achieved after surgery.

Patients who had secondary hyperparathyroidism or who had undergone previous neck exploration were excluded.

Ultrasound scan technique

The equipment used was a Hewlett-Packard (Andover, Massachusetts, USA) phased, steered array, with a 5·0 MHz transducer, combined with a dedicated stand-off or gelpack (Kitecko, 3M, Loughborough, UK). Significant limitations of the available equipment were the absence of a high frequency (7·5–10 MHz) transducer and lack of zoom facility when compared with the machine used in a previous study[8]. No attempt was made to standardize gain, or time compensated gain settings, each being optimized for every patient. Serial axial and transverse sections were obtained and patients were asked to perform deglutition during the procedure to maximize the chances of detecting lower tumours. No attempt was made to explore the mediastinum.

The diagnosis and localization were invariably decided during the course of the examination, and not by subsequent referral to the film record. All sections were obtained using the smallest practicable scale of display and suspect regions were recorded using film, reproducing the white-on-black video image.

Thallium scan technique

^{201}Thallium, administered as thallous chloride, accumulated in both thyroid and parathyroid tissue, and to a lesser extent in surrounding lean tissue. ^{99m}Tc-pertechnetate and, from 1 October 1985, ^{123}I-iodide was used to visualize the thyroid; iodide was preferred since it enabled thyroid images of good quality to be produced consistently.

^{123}I was given orally (10 MBq) the night before the scan. Anterior imaging was performed with a low energy, general purpose parallel hole collimator attached to a large field of view γ-camera (Siemens ZLC 7500, Sunbury-on-Thames, UK), and the data were transferred to a computer (Nodecrest Micas system, Byfleet, UK). The image data were collected in a 128 × 128 array covering a field of view 19 cm square which included the thyroid and the upper mediastinum.

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Table 1 *Comparison of localization by thallium and ultrasound scans*

	Total *n*	Helpful scans *n* (%)	Unhelpful scans *n* (%)	Misleading scans *n* (%)
Thallium scan	71	42 (59)	26 (37)	3 (4)
Ultrasound scan	68	23 (34)	41 (60)	4 (6)

Table 2 *Decision matrix for all glands by thallium and ultrasound scan irrespective of size or pathology*

		Pathological diagnosis		
		Positive	Negative	Total
Thallium diagnosis	Positive	34	18	52
	Negative	39	193	232
	Total	73	211	284
Ultrasound diagnosis	Positive	15	11	26
	Negative	55	191	246
	Total*	70	202	272

* Three patients were not assessable

Initially a 10 min dual image acquisition was performed in a window centred on the ^{123}I photopeak (159 keV), and in a lower energy window covering the ^{201}Tl photopeaks (69–80 keV) The latter image recorded cross-talk in the ^{201}Tl window from scattered ^{123}I γ-rays. Subsequently, 75 MBq of ^{201}Tl was injected intravenously. After 5 min a final image was acquired in the thallium window. The images were processed as follows: (1) the cross-talk image was subtracted from the thallium image; (2) background was removed from the resultant image, followed by a nine-point smooth; (3) a close-fitting region of interest was defined around the smoothed ^{123}I image of the thyroid to ensure that the thallium and iodine images were spatially coincident. The counts in the region of interest were recorded in both images to normalize the iodine thyroid to the same count total as the thallium thyroid; and (4) the normalized iodine image was subtracted from the thallium image. Any increased uptake of ^{201}Tl in parathyroid tissue was then obvious as a high contrast region of activity and, using the defined region of interest and a radioactive marker applied to the suprasternal notch, its position could be reported accurately

Analysis of results

A comparison was made between the operative findings and the results of the localization procedures, examining the influence of gland weight and comparing the accuracy of the scan modalities.

Assessment of the value of each localization procedure for an individual patient was made by examining whether the scan would have allowed the surgeon to pursue a policy of scan-directed unilateral cervical exploration.

Scan results were designated as follows: (1) helpful when an adenoma was correctly localized to one or both sides of the neck; (2) unhelpful when the scan failed to localize an adenoma or localized an adenoma to one side, while missing another adenoma on the contralateral side; and (3) misleading when the scan localized an adenoma to the incorrect side

All the data were analysed by a combination of the Mann–Whitney *U* test, decision matrix analysis and Bayes' Theorem, as described by McNeil and Adelstein[9].

Results

Of the 71 patients coming to first neck exploration 66 were found to have a single abnormal gland and two patients had multiple adenomas, with three and four gland disease respectively. The anatomical distributions of adenomas were. right upper, 9 glands, 12 per cent; left upper, 13 glands, 18 per cent; right lower, 26 glands, 36 per cent; left lower, 25 glands, 34 per cent. In all, 134 of a possible total of 193 remaining normal glands were identified. Three patients had no obvious parathyroid tissue, normal or otherwise, on neck exploration and were the only patients not made biochemically normal.

Three ultrasound scans were of poor technical quality owing to the obesity of the patients. Their results have, therefore, been excluded from the analysis. Their thallium scans remain valid and are included.

Comparison of the values of each scan modality for individual patients reveals thallium scanning to be more helpful than ultrasound (*Table 1*).

There were eight instances of conflict between scan results; in five the thallium scan was correct and in three the ultrasound scan was correct.

There were only ten instances of concordance in positive localization for both scans. In 14 cases neither scan identified any abnormal parathyroid tissue and in the remaining 36 paired scans only one modality identified abnormal parathyroid tissue.

The results for thallium and ultrasound localization were entered into a decision matrix including all glands, irrespective of size or pathology (*Table 2*).

In 66 patients with solitary adenomas examined by thallium scan accurate localization occurred in 33 patients. For the 63 patients with solitary adenomas examined by ultrasound scan successful localization occurred in only 13. Calculation of nosological probabilities allowed a direct comparison between the two scans (*Table 3*).

In the two patients with multigland disease and a total of seven abnormal glands, only one was localized by thallium and two by ultrasound.

Comparison of the weights of positively and negatively localized glands showed a clear relationship between the ability to localize and gland weight (*Table 4*)

Although not significant statistically, ultrasonography tended to be better at localizing the larger glands. The effect of gland weight on accuracy of localization was further analysed by studying glands weighing greater or less than either 500 mg or 1 g.

Thirty-eight adenomas weighing more than 1 g were examined by thallium scan and 36 by ultrasound scan; of these, 24 (63 per cent) and only 11 (31 per cent) were accurately localized by the two techniques respectively.

Table 3 *Nosological probabilities for all glands, irrespective of size, when localized by thallium and ultrasound scan*

	Ultrasound scan *n* (%)	Thallium scan *n* (%)
Sensitivity		
True positive	15/70 (21·4)	34/73 (46·6)
False positive	11/202 (5·4)	18/211 (8·5)
Specificity		
True negative	191/202 (94·5)	193/211 (91·5)
False negative	55/70 (78·6)	39/73 (53·4)
Accuracy (true positive and true negative)	206/272 (75·7)	227/284 (79·9)

Table 4 *Comparison of weight characteristics for positively and negatively localized glands, by thallium and ultrasound scan*

	n	Mean(s d.) weight (g)
Thallium		
Positively localized	34	3·35(4 25)*
Negatively localized	39	1·45(1·95)*
Ultrasound		
Positively localized	15	3·7 (4·4)†
Negatively localized	55	2·0 (3 0)†

* $P = 0\,004$, † $P = 0\,197$ by the Mann–Whitney *U* test, three patients were not assessable by ultrasound

For adenomas of less than 500 mg, 23 were examined by thallium scan and 22 by ultrasonography and the accuracy of localization was markedly diminished at 17 per cent and 18 per cent respectively. In those instances in which the presence of an adenoma weighing less than 500 mg was associated with a positive scan of either modality the localization was invariably accurate.

Discussion

These results indicate a lower degree of accuracy of parathyroid localization by ultrasonography compared with thallium scintigraphy. The results for ultrasonographic localization show a significant deterioration when compared with previously published data from this unit[8] and is probably explicable by the use of a newer and more sophisticated but less specialized machine which replaced the older, static B-mode unit. The newer technology associated with this unit was offset by the higher resolution afforded by a 7·5 MHz transducer, used in the older unit but unavailable to the newer machine, therefore limiting its value in cervical ultrasonography.

A sufficiently accurate localization procedure would allow confident preoperative prediction of pathology and a unilateral exploration. This advantage would be limited to patients with a solitary adenoma. In the series[1] of Thompson *et al.* four gland hyperplasia accounted for 15 per cent and multiple adenomas for 2·5 per cent of patients with primary hyperparathyroidism. The value of a unilateral exploration would be lost in these patients. Our data suggest that localization procedures are of particularly low value in those with multigland disease.

A scan-directed unilateral cervical approach, from these data, would lead to inadequate treatment; using thallium scans 41 per cent of patients would not be offered unilateral excision and the results for ultrasound scan are worse.

Thallium subtraction scintigraphy provides a moderately reliable means of preoperative localization for adenomas weighing more than 1 g. The surgeon is unlikely to need guidance in the identification of adenomas weighing over 1 g, however, and for both localization procedures, glands weighing 500 mg or less are consistently beyond the range of detection, both in our study and in others[5,8].

Could negative scans be useful? A negative scan might alert the surgeon to the possibility of a small adenoma or multiple gland disease. This would be unlikely, statistically speaking, to justify the expense incurred; in this series in only 19 out of 232 instances was an adenoma of less than 500 mg associated with a negative thallium scan at a specific site.

Combining the two scan results might allow certain identification of an adenoma where the scan results are concordant. This applied to only ten of 68 paired scans and in this group the mean weight of adenoma was 5·5 g. Tumours of this size should not be missed by the experienced parathyroid surgeon.

Parathyroid surgeons operating with a sound knowledge of the applied anatomy, embryology and gross pathology of the parathyroid gland, continue to achieve more than commendable results[1]. As Thompson states[10], to improve upon these by adding a preoperative localization procedure would require a scan with an extremely high sensitivity and specificity, which none of the current modalities possesses.

While we would not seek to denigrate the value of preoperative localization for patients undergoing reoperation, in which their role is proven[11], we would suggest that the expense and inconvenience of these techniques is not justified in those coming to first-time exploration for primary hyperparathyroidism.

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Infected false aneurysms in the groin of intravenous drug abusers

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The hazards of dealing with infected false femoral aneurysms resulting from intra-arterial narcotic injection are highlighted in six patients. Two patients were human immunodeficiency virus positive and three patients were hepatitis B surface antigen positive. Because of these infections exploration of groin swellings as presumed soft tissue abscesses is potentially hazardous without proper proximal vascular control. All patients underwent reconstruction following arterial ligation and five grafts became infected, with life threatening haemorrhage occurring in four patients. Five grafts have subsequently occluded or have been removed without loss of limb viability, although two patients have been regrafted. A high index of suspicion and assessment by a vascular surgeon, with angiography if indicated, is required in any intravenous drug abuser presenting with a groin swelling following injection. Because of the great risk of graft infection, it is suggested that ligation and debridement alone be carried out, with immediate arterial reconstruction only for non-viability.

Keywords: Femoral artery, aneurysm, drug abuse

Intravenous drug abuse is reaching epidemic proportions in inner city areas in the UK. Infected false aneurysm, arising from the common femoral artery as a result of intra-arterial injection, is an uncommon but serious complication of this practice The management of this problem is further complicated by the presence of human immunodeficiency virus (HIV) and hepatitis B virus infection in many patients. We report six patients with infected common femoral false aneurysm who demonstrate the potential problems

Case reports

Case 1

A 33-year-old man was admitted with a painful swelling in the left inguinal region. He was a known drug abuser who admitted to recent left groin injection. Examination revealed a tender indurated inflammatory mass which was non-pulsatile; the peripheral pulses were present Ultrasonography showed an intact femoral artery and arrangements were made for incision and drainage of a 'soft tissue abscess' under general anaesthetic. Only some serous fluid was obtained The following day his left leg became cyanosed, painful and mottled with absent pulses. He was HIV and hepatitis B surface antigen positive A vascular opinion was sought and a Seldinger arteriogram was performed which showed a false femoral aneurysm (*Figure 1*) He was taken to theatre and the aneurysm ligated proximally and distally In view of the non-viability of the limb before operation, an 8 mm polytetrafluoroethylene vascular graft was inserted from the left common iliac to the superficial femoral artery via a remote lateral tunnel, avoiding the infected groin. The graft functioned satisfactorily. Bacterial culture obtained at the time of operation revealed *Staphylococcus aureus* and the patient was treated with a prolonged course of flucloxacillin. The groin wound was treated with irrigation and he was discharged 20 days after admission with a healed wound and a functioning graft. After 12 months follow-up his graft continues to function with no evidence of infection and his drug habit is under control

Case 2

A 28-year-old man was admitted with a history of a recent development of a groin swelling following an attempted femoral vein injection of heroin. At operation the swelling proved to be a false aneurysm of the femoral artery which was repaired using a vein patch on its anterior aspect His HIV status was negative but he was hepatitis B surface antigen positive. Culture of material from the aneurysm grew *Staphylococcus aureus* and the patient was given flucloxacillin. Eleven days after operation the patient had a massive haemorrhage from the groin while in the ward. Following resuscitation he was taken back to theatre. The common femoral artery was ligated and reconstruction performed using an iliofemoral Dacron® (DuPont) graft. The wound was then irrigated with cefuroxime. This graft became infected and 3 weeks following insertion it was ligated and an iliopopliteal graft using 6 mm polytetrafluoroethylene inserted, routed via the obturator foramen (*Figure 2*). One week later the Dacron graft was removed. At follow-up the obturator graft continues to function satisfactorily and his groin wound is healed, but he continues to abuse heroin, injecting into his right arm and left groin.

Case 3

A 28-year-old man was admitted with an 8-day history of a fluctuant, non-pulsatile, tender swelling in the left groin, following a self administered injection. Distal pulses were present. He admitted to

Figure 1 *Angiogram from case 1 showing false aneurysm (arrowed) arising from the left common femoral artery*

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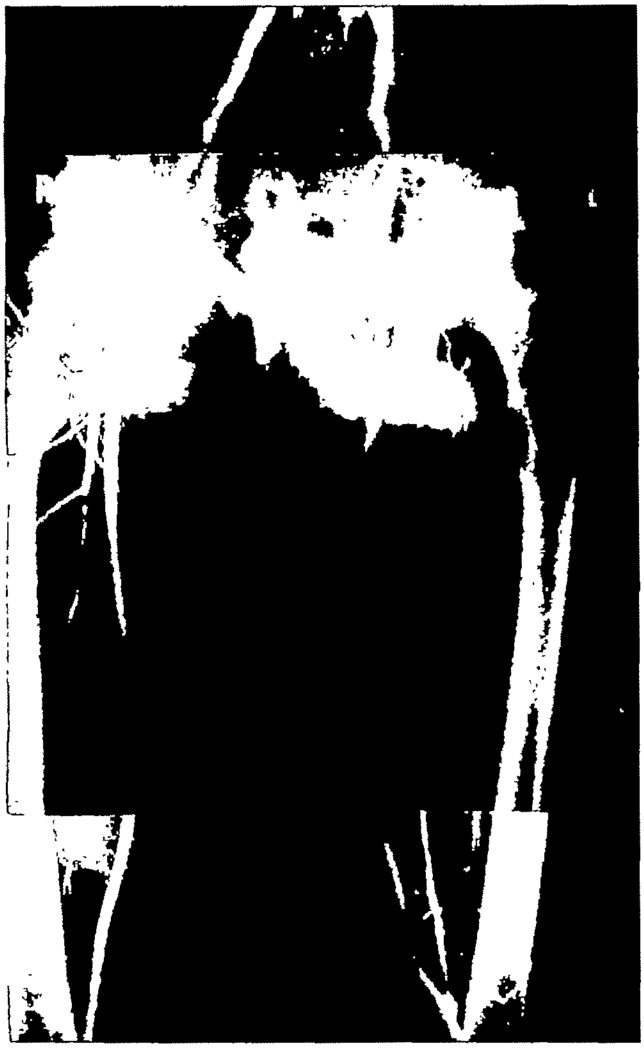

Figure 2 *Angiogram from case 2 showing functioning iliopopliteal obturator graft*

intravenous drug abuse over the previous 4 years His HIV and hepatitis B surface antigen status were negative On the assumption that this was a soft tissue abscess, he was taken to theatre with the intention of drainage, but on incision a large quantity of fresh blood was encountered and the advice of a vascular surgeon was sought An infected false aneurysm was confirmed with extension of the infective process retroperitoneally as far as the aortic bifurcation. The common femoral artery, which was extremely friable, was excised and reconstituted using autogenous vein from the external iliac artery to the common femoral artery bifurcation The wound was irrigated with cefuroxime; culture grew *Staphylococcus aureus* and systemic flucloxacillin was prescribed. Despite these measures the groin wound broke down due to infection and, on the fifteenth day after operation, he had a sudden profuse haemorrhage in the ward. He was resuscitated and taken to theatre but no obvious bleeding point was found, both proximal and distal vein graft anastomoses being intact One week later he had a further episode of profuse haemorrhage with hypotension and the vein graft was ligated. A further massive bleed occurred 10 days later, once again requiring suture ligation There was no further bleeding and, despite having ligated the graft, the leg remained viable. Necrosis of the wound occurred requiring debridement on several occasions An intravenous digital subtraction angiogram showed filling of superficial femoral and profunda femoris arteries via extensive collaterals derived from the circumflex iliac and internal iliac artery tributaries (*Figure 3*). He was discharged 8 weeks after admission having been fitted with a caliper to assist hip flexion and knee extension as he had developed iliopsoas necrosis and quadriceps femoris weakness during the course of his illness

Case 4

A 36-year-old man was admitted with an ischaemic right leg and a pulsatile mass in the right groin No pulses were palpable in the right leg. He admitted to intravenous drug abuse over the previous 10 years He was taken to theatre and a right common femoral false aneurysm confirmed. The common femoral artery was excised and the circulation restored using a tube of 8 mm polytetrafluoroethylene from the external iliac artery to the common femoral bifurcation Swabs taken at the time of operation grew *Staphylococcus aureus* and he was given fluxcloxacillin. He was discharged 10 days later with a healed wound and referred to a drug withdrawal programme The patient was readmitted 2 months later with a persistent discharge from the right groin and a metastatic abscess on his foot. Drainage of the abscess and culture of the pus revealed *Staphylococcus aureus* and he was given flucloxacillin. His graft at this time was functioning satisfactorily. He took his own discharge and failed to attend the outpatient clinic He returned 2 years after the initial episode complaining of claudication at 50 m in the right leg and a discharge from the right groin There were no pulses present in the leg, culture from the groin revealed *Staphylococcus aureus*, and an intravenous digital subtraction angiogram confirmed that the graft had occluded but with reconstitution of the profunda and superficial femoral arteries via excellent collaterals. The graft was removed without further reconstruction

Case 5

A 31-year-old male drug abuser was admitted with swelling of both legs and a mass in the left groin following injection into both groins. He was HIV and hepatitis B surface antigen positive It was considered at that time that the groin mass might be a false aneurysm. He was commenced on antibiotics but took his own discharge shortly after admission. Some 4 months later he was readmitted with profuse bleeding from the left groin. He was hypotensive on admission, with a pulsatile mass over the left femoral artery. Haemoglobin was 6·9 g/dl Following resuscitation he was taken to theatre and a false aneurysm excised with reconstruction using an 8 mm polytetrafluoroethylene iliofemoral bypass He was discharged 8 days after admission and was subsequently lost to follow-up He was readmitted 1 year later with a discharging abscess in the left groin, the base of which contained graft material. An arteriogram showed the graft to be occluded No further procedure was undertaken but 1 month later he returned with a profuse bleed A false aneurysm of the external iliac artery at the proximal

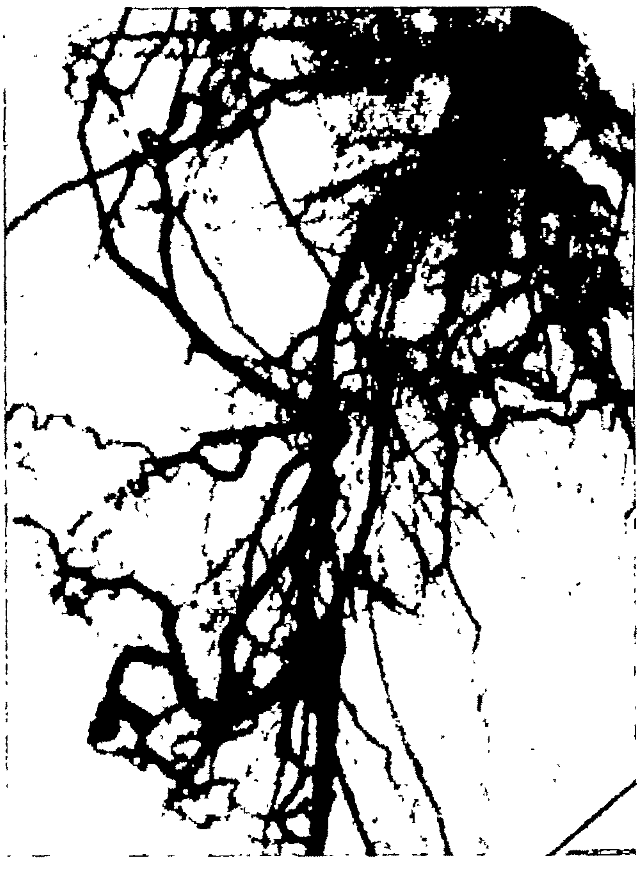

Figure 3 *Angiogram from case 3 showing occlusion of graft with extensive collateral circulation maintaining limb viability*

anastomosis was oversewn and the graft removed. A week later he had a further haemorrhage requiring oversewing of the bleeding area. Culture, obtained at his initial presentation and throughout, revealed a mixed growth of *Staphylococcus aureus, Streptococcus faecalis* and mixed anaerobes Following a prolonged hospital course the wound healed with no further bleeding and a viable limb resulted. Following discharge this patient was lost to follow-up.

Case 6

A 26-year-old man was admitted as an emergency with an inflamed pulsatile mass in the right groin where he had been attempting to inject drugs intravenously. He was HIV and hepatitis B surface antigen negative. The limb was viable. He was taken to theatre and the presence of an infected false aneurysm confirmed, with disruption of an extremely friable common femoral artery. This was ligated and an iliofemoral bypass performed using 8 mm polytetrafluoroethylene. He made satisfactory progress but discharged himself on the sixth day after operation. He failed to attend the outpatient clinic but was readmitted 6 weeks later as an emergency with severe haemorrhage from the right groin. He was taken immediately to theatre following resuscitation and an infected graft removed and the vessels ligated In order to maintain circulation to the right leg, an iliopopliteal bypass via the obturator foramen was performed using 6 mm polytetrafluoroethylene Once again he made good progress until he took his own discharge. He has since been lost to follow-up.

Discussion

In recent years, in parallel with the increased abuse of narcotics, particularly of intravenous heroin, a number of drug related diseases have been recognized including infected false aneurysms. The pathogenesis of this lesion is the introduction of infected material by non-sterile technique combined with trauma from inadvertent arterial puncture or even deliberate arterial puncture when peripheral intravenous sites have thrombosed. These patients present with a painful, tender, inflamed mass adjacent to a major blood vessel. Pulsation of the mass may be difficult to appreciate because of soft tissue swelling; the peripheral pulses may be present. Such lesions may be mistaken for soft tissue abscesses, lymphadenitis or cellulitis, and aspiration or incision and drainage attempted. These aneurysms have the potential for torrential, uncontrollable haemorrhage, especially if encountered by the unwary surgeon expecting to find a simple soft tissue abscess. This can be dangerous not only for the patient but also for medical and nursing attendants because of HIV and hepatitis B infection The incidence of HIV infection in intravenous drug addicts has been estimated to be between 5 and 85 per cent[1,2]. Although only two patients in our series had definite HIV infection, three showed evidence of previous hepatitis exposure. It is imperative that all such high risk patients are treated with full precautions to minimize the risk of HIV and hepatitis infection and to understand that current routine precautions may not prevent contamination of attending staff from a major arterial haemorrhage. It is essential that any known intravenous drug abuser with a swelling overlying a major vessel which has been used for injection should be considered to have a false aneurysm. The practice of blind exploration which was undertaken in three of the patients described must be condemned and all patients should be referred to a vascular surgeon for angiography before any surgical procedure.

The optimal treatment of infected false aneurysm in these patients includes parenteral antibiotics, extensive debridement, control of haemorrhage and restoration of distal circulation when necessary. Blood cultures are usually positive, the common organism being *Staphylococcus aureus*[3] although other organisms may be present[4]. All six patients in the present series grew *Staphylococcus aureus* and so initial antibiotic therapy, although empirical, should provide broad cover with specific inclusion of an antistaphylococcal agent. Surgical treatment is directed initially at control of haemorrhage and debridement of all infected and necrotic tissue. Proximal control of the aneurysm should be obtained by ligation of the external iliac artery via an extraperitoneal or transperitoneal supra-inguinal approach. High ligation avoids the need to attempt to ligate an inflamed friable vessel. Distal control can then be obtained by opening the aneurysm and suture ligating from within. Having controlled haemorrhage and debrided infected tissue, attention is turned to the need to restore distal circulation.

Graft infection is a major problem which may occur early, through contamination from the original site, or late through subsequent use of the graft for injection by the patient. Early graft infection occurred in five patients and resulted in major haemorrhage in four. These haemorrhages occurred in the ward as a result of graft–artery disruption due to infection and were dangerous to patients and staff. Furthermore, lack of ready intravenous access makes resuscitation difficult without central venous cannulation.

That three patients have viable limbs despite infection and removal of the graft, or graft closure, suggests that simple debridement and ligation together with systemic antibiotics may have been sufficient and that there was no need for reconstruction. Such an approach was advocated by Feldman and Beurger[3] who reported success with 'selective delayed revascularization' following ligation in 30 patients, with only six reconstructions required between 5 days and 2 months later. Limb viability must be assessed carefully. Although a limb may be considered non-viable before operation, the presence of sepsis, haematoma, and aneurysm may exaggerate the ischaemia because of venous compression and the failure of collateral arterial circulation by tissue tension. Viability should be reassessed following drainage of sepsis and debridement. If the limb improves, antibiotics should be continued both systemically and by local irrigation. Vascular reconstruction should only be carried out when the limb remains non-viable and should be performed away from the site of infection. Autogenous material is seldom available, and even when used is not immune from the risk of infection (case 3). Synthetic grafts should be placed in an extra-anatomical plane either by using a lateral iliac to superficial femoral artery bypass[5], or using the obturator foramen[6]. When the ipsilateral iliac artery is not suitable because of gross extraperitoneal extension of the sepsis, the contralateral femoral artery can be used for inflow to a suprapubic crossover lying subcutaneously or extraperitoneally, avoiding the infected region. Alternatively the transperineal route may be used[7,8]. When necessary late reconstruction should be performed after sepsis has been eradicated.

Surgical treatment of infected false aneurysms in drug addicts should not be delayed and early referral to a vascular surgeon is advisable. An angiogram should be performed, particularly if there is doubt about arterial integrity. On the basis of our experience, if a false aneurysm is present and the limb is viable, ligation, drainage and debridement is the emergency procedure of choice. If, following ligation, the limb remains viable, conservative treatment should be continued with appropriate antibiotics, which should include an antistaphylococcal agent. These may be given systemically and by local infusion to eliminate the danger of graft infection and delayed haemorrhage. If the limb appears non-viable and fails to recover following debridement, or becomes non-viable after ligation, revascularization may be required, accepting the risk of graft infection. This should be performed if possible by an extra-anatomical route. Where this is not possible an *in situ* graft is the only alternative. In such circumstances infection of the graft and haemorrhage seems inevitable and it may be argued that a policy of planned graft occlusion over a period of 10 days or so might allow collaterals to develop and so render removal of such a temporary graft safe, avoiding the risk of subsequent haemorrhage.

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Short notes

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Intra-arterial injection of oral medication in HIV positive drug addicts

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The number of parenteral drug abusers continues to increase and this has led to an escalation in the frequency of problems associated with self-injection.

Venous access becomes increasingly difficult for the long-term addict as the superficial veins become sclerosed by repeated, non-sterile, use and the addict is forced to seek alternative injection sites such as the groin. This can lead to the 'accidental' intra-arterial self-administration of drugs. Intravenous drugs are hard to obtain and expensive; this has led to the increasingly common and worrying practice of parenteral injection of crushed oral drug preparations. Furthermore, the spread of human immunodeficiency virus (HIV) infection amongst the drug addict population presents formidable management problems when vascular complications develop.

The presentation of several HIV positive patients who had sustained arterial trauma from injection of crushed 'oral' drugs within a short time prompted this review.

Patients and methods

Over the past 6 months the Vascular Surgery Unit of the Royal Infirmary of Edinburgh has been referred eight parenteral drug abusers, all HIV positive, who had self-administered crushed oral medication into their arteries. Ischaemia secondary to the intra-arterial injection of oral medication had only been seen once or twice in each of the previous 3 years.

These patients were all young men, mean age 29 years, who were long-term addicts. Six had 'accidentally' injected the femoral artery and the other two cases had brachial and ulnar artery involvement respectively. In each the medication injected was a narcotic analgesic, most commonly buprenorphine Amputation was necessary in only two cases, and was associated with delayed referral and major arterial occlusion. Relevant clinical details are listed for each patient in *Table 1*

Discussion

Mechanism of ischaemia

Distal ischaemia may occur following the intra-arterial injection of a wide range of abused drugs, although the risk of tissue ischaemia following the injection of oral preparations appears to be even greater. The mechanism by which this ischaemia occurs has been studied by several workers. Vasospasm is unlikely to be the mechanism causing the ischaemia, as animal studies have shown that typically abused drugs actually cause vasodilatation[1]. It is probable that tissue damage is due to microvascular embolization by filling agents such as milk powder in illegally obtained addictive preparations and corn starch or talcum powder in parenterally used oral preparations[1]. The extent of the damage depends on the size and number of particles injected Platelet aggregation does not appear to be the cause of the microvascular occlusion[2] and Buckspan and his colleagues have suggested that the occlusion may be the result of a direct toxic effect on small distal vessels causing vasculitis, sludging and localized thrombosis[3]. Intimal damage at the site of injection might account for the major arterial occlusion seen in cases 1 and 7 (*Table 1*) but could not produce the type of distal damage seen in the other six cases

Site of injury and outcome

The vascular hazards of injection into the femoral triangle have already been recognized. Mycotic aneurysms, septic thrombophlebitis and arteriovenous fistulae have all been described[4] Acute ischaemia appears to be a less frequent complication, although cases of penile and scrotal gangrene secondary to accidental femoral artery injection have been reported[5]. Distal or major limb gangrene appears less common and only a few sporadic reports of digital gangrene secondary to intra-arterial injection have appeared in the literature[6,7] The hazards of injection into the femoral triangle and the relative rarity of tissue necrosis are shown in our small series. Six of the eight patients presenting with ischaemic complications had injected into the femoral triangle with only one major limb amputation as a result (case 1)

Management

The complex pathophysiology of such ischaemia makes management difficult. As vasospasm does not appear to play a major part in the mechanism of ischaemia, the often recommended

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Table 1 *Case summaries*

Case number	Age (years)	Drug used	Artery injected	Distal pulses	Duration (h)	Final outcome
1	30	Dihydrocodeine	Femoral	Absent	16	Hip disarticulation and renal failure
2	33	Buprenorphine	Femoral	Present	3	Localized thigh muscle necrosis. TOD*
3	27	Buprenorphine	Femoral	Present	6	Foot mottling. TOD*
4	27	Dihydrocodeine	Femoral	Present	8	Toes/forefoot mottling. TOD*
5	24	Buprenorphine	Femoral	Present	5	Transient toe mottling
6	31	Dextropropoxyphene	Femoral	Present	10	Foot mottling. TOD*
7	37	Dipipanone hydrochloride	Ulnar	Not applicable	5	Ischaemia of lateral three fingers, recovery at 1 week
8	28	Dipipanone hydrochloride	Brachial	Absent	36	Gangrene of fingers. Amputation of four finger tips

*TOD, took own discharge

treatment using pharmacological vasodilatation or sympathetic nerve block[8] is likely to confer little benefit. Similarly, as platelet aggregation appears to be unimportant, antiplatelet drugs have not been shown to offer any therapeutic benefit[9].

Management of ischaemia following the intra-arterial injection of drugs should be based on the presence or absence of distal pulses. Where there is evidence of large vessel involvement (absence of distal pulses) an early angiogram is indicated, otherwise the distal ischaemia should be managed by intravenous heparin to maintain patent collaterals and prevent the propagation of thrombus. As there is some experimental evidence that intra-arterial steroids may confer benefit by counteracting the putative small vessel vasculitis[3], these should be routinely administered.

Two other problems in management are demonstrated here. Firstly, all our patients were found to be HIV positive. Of all drug abusers screened so far by the Edinburgh Blood Transfusion Service 60 per cent have been found to be HIV positive, but in this group of long-term abusers who have 'run out' of ordinary vascular access sites the proportion is much higher. Angiography, vascular reconstruction and amputation in HIV positive patients presents a challenge, not only because of the risk to medical and paramedical personnel, but also because of the impaired response to infection and poor healing found in the later stages of the disease. This was well illustrated in case 1 where delayed healing, persistent wound discharge and osteomyelitis of the acetabulum occurred after hind quarter amputation.

Secondly, the problems of management may be compounded by the patient's own addiction. Both cases which eventually required amputation presented late at 16 and 36 h after injection. Cooperation may be lacking, even after a patient has presented to hospital. Half of the patients in this series took their own discharge from hospital against medical advice within 48 h of admission.

There appears to be an increase in the number of patients presenting with ischaemia secondary to the intra-arterial injection of oral medication. Although most are related to injection in the femoral triangle, major arterial occlusion is uncommon and so most patients can be managed conservatively. In this small series significant tissue loss was only associated with major arterial occlusion

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Hepatic haemodynamic changes after portacaval anastomosis in normal, cirrhotic and chronic prehepatic portally hypertensive rats

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Radioactive microspheres were used to determine the hepatic haemodynamic response to portacaval anastomosis in normal, cirrhotic and chronic prehepatic portally hypertensive rats 20 days after operation, and in normal rats 2 months after operation. After 20 days portacaval anastomosis caused a decrease in liver mass only in normal and cirrhotic animals, whereas hepatic arterial blood flow per unit of mass increased in normal (+488 per cent), cirrhotic (+191 per cent) and prehepatic portally hypertensive rats (+133 per cent). Despite these facts, animals with portacaval anastomosis showed a reduced hepatic total perfusion (arterial plus portal inflow) per unit of mass with respect to controls in normal (−53 per cent) and cirrhotic rats (−68 per cent), but not in those with prehepatic portal hypertension. Comparing studies carried out at 2 months with those performed 20 days after portacaval anastomosis in normal rats, some recovery of liver mass and total liver blood flow was observed. In conclusion, portacaval anastomosis produced a limited increase in hepatic arterial blood flow which was unable to preserve liver mass and its total perfusion in normal and cirrhotic animals. In contrast, portacaval anastomosis did not significantly alter liver mass or its perfusion in animals with chronic prehepatic portal hypertension, as both values were previously diminished in controls. Thus, the risk of liver failure after portacaval anastomosis is higher in normal and cirrhotic rats than in those with chronic prehepatic portal hypertension.

Keywords: Hepatic haemodynamics, portacaval anastomosis, cirrhosis, prehepatic portal hypertension, rats

Portacaval anastomosis in cirrhotic patients is accompanied by a high incidence of liver failure, which seems to be related to a decreased hepatic blood flow. Proponents of selective portal–systemic shunts have stressed the need to preserve hepatic blood flow in such patients. Assessment of hepatic haemodynamics is difficult because of the dual blood supply of the liver, and the conventional method used in man and animals based on Fick's principle gives limited information. Radiolabelled microspheres provide a means of assessing experimentally the hepatic portal and arterial blood flow, as well as the magnitude of portal–systemic shunting[1–3]. The aim of the present study was to assess the hepatic haemodynamic changes that portacaval anastomosis produces in normal rats and those with cirrhotic and chronic prehepatic portal hypertension, and to assess the adaptation of a normal or diseased liver to portal blood flow deprivation.

Materials and methods

Studies were completed in 50 male Wistar rats divided into three groups: normal ($n=20$), cirrhotic ($n=16$) and chronic prehepatic portal hypertension ($n=14$). Rats had a mean(s.e.m.) weight of 304·6 (10·4)g at the time of surgical portacaval anastomosis, without differences between groups. Cirrhosis of the liver was induced in 150 g rats by a combined treatment with oral phenobarbitone and inhaled carbon tetrachloride, as previously described[4,5]. Treatment was continued for 3 months but stopped 1 week before surgical intervention. At the end of the experiment, a small portion of liver was studied histologically, and only animals showing grade V hepatopathy according to Gerber and Popper[6] were considered cirrhotic. These animals developed portal hypertension with a moderately developed collateral circulation as shown by contrast radiology. Chronic prehepatic portal hypertension was progressively induced in 150 g rats as previously described[7] by placing, through a small laparotomy, a PE50 catheter alongside the length of the portal vein and then tying a 3/0 ligature tightly around both catheter and vein. The catheter was removed and, as it was about the diameter of the portal vein of a 150 g rat, the vein re-expanded inside the ligature without stenosis. As the animals grew, the portal vein became progressively constricted, and they developed prehepatic portal hypertension with a marked collateral circulation, as shown by radiological examination, within 3 months.

An end-to-side portacaval anastomosis was performed in half of the animals in each group as described by Lee and Fisher[8]. Under ether anaesthesia, the abdomen was opened through a midline incision, the portal vein and inferior vena cava were dissected, clamped, sectioned or opened, and anastomosed with an 8/0 nylon running suture. Clamping time was about 12 min. Immediate patency of the shunt was assessed. Dissection was difficult in the prehepatic portally hypertensive rats owing to extensive collateral circulation and bleeding, and an intraoperative bolus of vasopressin (1 μg/kg body-weight intravenously) was necessary. The perioperative mortality rate was 19 per cent in normal, 23 per cent in cirrhotic and 46 per cent in chronic prehepatic portally hypertensive rats. In the remaining half of the animals (which served as controls in each group) a sham operation was performed, in which the portal vein and inferior vena cava were dissected and clamped for 12 min.

Hepatic haemodynamics were assessed 20 days after portacaval anastomosis or sham operation, using the radioactive microspheres method with reference sampling as described in previous reports from this laboratory[1,2] and by Groszmann *et al.*[3]. Animals were anaesthe-

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tized with sodium pentobarbital (Nembutal®, Abbott, Chicago, USA, 40 mg/kg body-weight), and rectal temperature was maintained at 37°C with a heating lamp. The left femoral and right carotid arteries were cannulated, connected to pressure transducers (Statham Instruments, Hato Rey, Puerto Rico) and arterial pressure was permanently recorded (Beckmann Instruments, Schiller Park, Illinois, USA). The right carotid catheter was advanced into the left ventricle during continuous pressure monitoring for systemic microsphere injection. A catheter was inserted into the splenic pulp, through a small paramedian incision, for splenic pressure monitoring (as an estimate of portal venous pressure) and portal microsphere injection. Once animals had stabilized, a reference sample was withdrawn from the femoral artery catheter at a rate of 1 ml/min for 1 min. At 15 s from beginning withdrawal of the reference sample, approximately 40 000 polymeric resin, ^{57}Co-labelled, 15 µm microspheres (New England Nuclear, Boston, Massachusetts, USA) were injected into the left ventricle over 15 s, the catheter being immediately rinsed with 0·2 ml isotonic saline. Reference sample volume was replaced as saline and arterial pressure was reassessed. Portal–systemic shunting was measured as previously described[2,3], using an intrasplenic injection of approximately 30 000 ^{113}Sn-labelled microspheres over 20 s. Long-term patency of the portacaval anastomosis was then assessed, and only animals with patent shunts were included in the study. Rats were killed with intraventricular potassium chloride, and the abdominal organs and lungs were dissected, weighed and counted for ^{57}Co and ^{113}Sn radioactivity in a two channel γ-counter. Corrections were made for the spillover of the ^{113}Sn energy into the ^{57}Co channel.

To assess the stability of the hepatic haemodynamic changes after portacaval anastomosis in normal rats over a longer period of time, another group of seven normal rats 317(9)g in weight was operated on to perform a portacaval anastomosis as has been described, the haemodynamic study being carried out 2 months later.

Haemodynamic parameters were calculated using previously reported formulae[2,3]. Arterial organ blood flow (ml/min) was given by [organ radioactivity (c.p.m.) × reference blood flow(ml/min)]/reference blood flow radioactivity (c.p.m.), and was expressed per gram of tissue. Portal–systemic shunting rate (%) was given by [lung radioactivity (c.p.m.)/(lung + liver) radioactivity (c.p.m.)] × 100. Portal venous inflow was calculated as the sum of arterial blood flow to stomach, spleen, intestines and mesentery, that is the amount of blood entering the portal system, and was expressed per 100 g body-weight. Hepatic portal blood flow (ml/min) was given by portal venous inflow (ml/min) – [portal venous inflow (ml/min) × (portal–systemic shunting rate/100)], and was expressed per gram of liver. Hepatic total blood flow was the sum of arterial and portal blood flow, and was expressed per gram of liver. Portal venous resistance (or portocollateral venous resistance in the presence of collateral circulation) (dyn s cm^{-5} × 10^{4}) was given by [pressure gradient (mmHg) × 80]/portal venous inflow (ml/min). Central venous pressure was considered to be zero since when it was measured it ranged between 0 and 1 mmHg. Thus, pressure gradient was taken to be the same as the portal pressure.

Results are expressed as mean (s.e.m.). Comparison between means was performed using an analysis of variance test. Values of $P < 0·05$ were considered statistically significant.

Results

Results of studies carried out 20 days after operation are shown in *Table 1* (differences between the controls of each group), and in *Tables 2–4* (effects of portacaval anastomosis on normal, portal vein constricted and cirrhotic rats). In control rats the highest liver weight was observed in the cirrhotic rats and the lowest in the portal vein constricted animals. This liver weight decreased after portacaval anastomosis in normal rats (–29 per cent) and cirrhotic (–28 per cent) but not in those with portal vein constriction.

Both control cirrhotic and control portal vein constricted rats showed portal hypertension as demonstrated by the portal pressure measurements; those values returned to normal values after performing a portacaval anastomosis. Portocollateral venous resistance in controls was much greater in rats with portal stenosis than in the other groups, while cirrhotic rats showed only a slight elevation. Portal venous inflow (per 100 g body-weight) of controls was higher in cirrhotic than in normal rats, reaching its lowest value in the portal vein constricted animals. This reflects the hyperdynamic splanchnic circulation developed in control cirrhotic rats. After portacaval anastomosis, the portal venous inflow of these cirrhotic rats remained

Table 1 *Hepatic haemodynamics in control sham operated rats of every group, 20 days after operation*

	Normal	Portal constriction	Cirrhosis
Liver weight (g)	9·9 (0·5)	8·8 (0·4)*	10·9 (0·5)*
Portal pressure (mmHg)	8·5 (0·8)	14·7 (1·5)*	14·2 (0·8)*
Portal venous resistance (dyn s cm^{-5} × 10^{4})	3·9 (0·9)	24·8 (4·6)*	4·3 (0·2)
Portal venous inflow (ml/min/100 gBW)	5·1 (0·4)	2·3 (0·4)*	7·9 (0·6)*
Portal–systemic shunting rate (% PVI)	0·26 (0·06)	72·1 (12·0)*	2·8 (0·3)*
Hepatic portal blood flow (ml/min/g)	1·6 (0·07)	0·2 (0·03)*	2·35 (0.3)*
Hepatic arterial blood flow (ml/min/g)	0.17 (0·02)	0·54 (0·1)*	0·5 (0·05)*
Hepatic total blood flow (ml/min/g)	1·76 (0·2)	0·74 (0·1)*	2·8 (0·36)*

Values are mean (s.e.m.). Analysis of variance, * $P < 0·05$ respect to sham operated normal rats. BW, body-weight. PVI, portal venous inflow

Table 2 *Hepatic haemodynamics in normal rats with or without portacaval anastomosis*

	Control	Portacaval anastomosis
Liver weight (g)	9·9 (0·5)	6·8 (0·3)*
Portal pressure (mmHg)	8·5 (0·8)	9·9 (1·3)
Portal venous resistance (dyn s cm^{-5} × 10^{4})	3·9 (0·9)	3·7 (0·7)
Portal venous inflow (ml/min/100 gBW)	5·1 (0·4)	8·3 (1·1)*
Portal-systemic shunting rate (% PVI)	0·26 (0·06)	98·3 (3·2)*
Hepatic portal blood flow (ml/min/g)	1·6 (0·07)	None
Hepatic arterial blood flow (ml/min/g)	0·17 (0·02)	0·83 (0·1)*
Hepatic total blood flow (ml/min/g)	1·76 (0·2)	0·83 (0·1)*

Values (mean (s.e.m.)) recorded 20 days after operation. Analysis of variance, * $P < 0·05$. BW, body-weight. PVI, portal venous inflow

Table 3 *Hepatic haemodynamics in cirrhotic rats with or without portacaval anastomosis*

	Control	Portacaval anastomosis
Liver weight (g)	10·9 (0·5)	7·8 (0·4)*
Portal pressure (mmHg)	14·2 (0·8)	7·1 (0·6)*
Portal venous resistance (dyn s cm^{-5} × 10^{4})	4·3 (0·2)	2·6 (0·4)*
Portal venous inflow (ml/min/100 gBW)	7·9 (0·6)	7·4 (1·2)
Portal-systemic shunting rate (% PVI)	2·8 (0·3)	98·7 (4·5)*
Hepatic portal blood flow (ml/min/g)	2·35 (0·3)	None
Hepatic arterial blood flow (ml/min/g)	0·5 (0·05)	0·91 (0·16)*
Hepatic total blood flow (ml/min/g)	2·8 (0·36)	0·9 (0·16)*

Values (mean (s.e.m.)) recorded 20 days after operation. Analysis of variance, * $P < 0·05$. BW, body-weight. PVI, portal venous inflow

Table 4 *Hepatic haemodynamics in portal vein constricted rats with or without portacaval anastomosis*

	Control	Portacaval anastomosis
Liver weight (g)	8·8 (0·4)	8·9 (0·5)
Portal pressure (mmHg)	14·7 (1·5)	10·2 (1·5)*
Portal venous resistance (dyn s cm^{-5} × 10^{4})	24·8 (4·6)	10·8 (2·3)*
Portal venous inflow (ml/min/100 gBW)	2·3 (0·4)	2·7 (0·2)
Portal-systemic shunting rate (% PVI)	72·1 (12·0)	99·1 (4·3)*
Hepatic portal blood flow (ml/min/g)	0·2 (0·03)	None
Hepatic arterial blood flow (ml/min/g)	0·54 (0·1)	0·72 (0·06)*
Hepatic total blood flow (ml/min/g)	0·74 (0·1)	0·72 (0·06)

Values (mean (s.e.m.)) recorded 20 days after operation. Analysis of variance, * $P < 0·05$. BW, body-weight. PVI, portal venous inflow

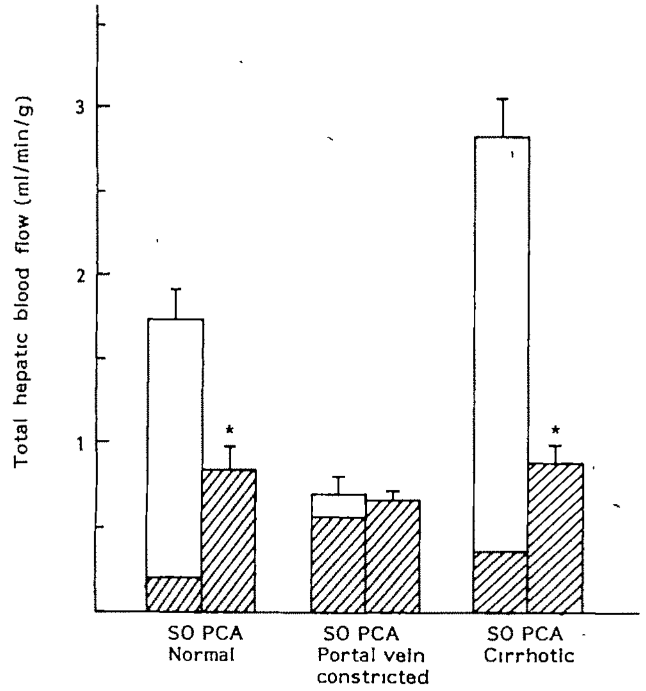

Figure 1 *Total hepatic blood flow per unit mass of liver in normal, chronic portal vein constricted and cirrhotic rats after sham operation (SO) or portacaval anastomosis (PCA).* □, *portal component,* ■, *arterial component.* * *Analysis of variance,* $P<0{\cdot}05$

Table 5 *Hepatic haemodynamics in normal rats at 20 days or 2 months after portacaval anastomosis*

	Portocaval anastomosis	
	20 days	2 months
Liver weight (g)	6·8 (0·43)	7·94 (0·41)*
Portal pressure (mmHg)	9·8 (1·3)	11·5 (1·5)
Portal venous inflow (ml/min/100 gBW)	8·3 (1·1)	10·7 (1·9)
Hepatic arterial blood flow (ml/min/g)	0·83 (0·15)	0·88 (0·13)

Values (mean (s.e.m.)). Analysis of variance, $^*P<0{\cdot}05$ BW, bodyweight

unchanged, whereas that of normal rats increased to reach a similar level of hyperdynamic splanchnic circulation. Portal venous inflow remained low after portacaval anastomosis in animals with portal stenosis. Portal–systemic shunting in controls was negligible in normal rats, and much higher in portal vein constricted rats than in cirrhotic animals. After performing a portacaval anastomosis, portal–systemic shunting was obviously complete in every group. The hepatic portal blood flow (per unit of liver mass) of controls was higher in cirrhotic than in normal animals, in spite of the moderate degree of portal–systemic shunting rate showed by the former. Hepatic portal blood flow was strikingly low in portal vein constricted rats After portacaval anastomosis, hepatic portal blood flow was absent in all groups.

Control cirrhotic and portal stenosed rats had a higher hepatic arterial blood flow (per unit of liver mass) than normal rats. After portacaval anastomosis, hepatic arterial blood flow increased to +133 per cent in portal vein constricted, to +192 per cent in cirrhotic, and to +488 per cent in normal rats. The hepatic total blood flow (arterial plus portal), per unit of liver mass, of controls (*Figure 1*) was higher in cirrhotic and lower in portal vein constricted rats. After portacaval anastomosis, the hepatic total blood flow, which depended in such circumstances exclusively on arterial blood supply, decreased markedly in cirrhotic (−68 per cent) and in normal animals (−53 per cent), whereas it remained nearly unchanged in rats with portal stenosis (−3 per cent).

Results of studies performed in normal rats 2 months after portacaval anastomosis (*Table 5*) showed that splanchnic circulation (as estimated by the portal venous inflow) continued to be hyperdynamic, and portal pressure did not change significantly. The hepatic arterial blood flow per unit of liver mass (hepatic total blood flow) remained steady around the value previously reached 20 days after operation, although liver mass was higher. This implies a net increase of flow through the hepatic artery.

Discussion

The two experimental models of portal hypertension used in the present study are associated with great differences in hepatic haemodynamics when compared with control sham operated groups. In cirrhosis, portal pressure increases in relation to a moderately elevated portocollateral venous resistance and as a result of a marked increase in portal venous inflow; this reflects a hyperdynamic splanchnic circulation only about 3 per cent of which is shunted to the systemic circulation. Other authors have reported such a hyperdynamic splanchnic circulation in experimental[2,3] and human cirrhosis[9], emphasizing a 'forward' component of cirrhotic portal hypertension. On the other hand, chronic progressive constriction of the portal vein increases portal pressure exclusively in relation to the great elevation in portocollateral venous resistance, portal venous inflow becoming scarce and with shunting of approximately 72 per cent of portal blood to the systemic circulation (the 'backward component of portal hypertension'). Collateral shunting veins are thus high resistance pathways The important finding in control groups is that portal perfusion of the liver is increased in rats with toxic cirrhosis and markedly decreased in rats with progressive prehepatic portal hypertension.

As our results show, the hepatic artery has the ability to compensate to some extent the loss in portal perfusion of the liver, regardless of whether the latter is caused by spontaneous or surgical portal–systemic shunts. By the total supression of portal blood flow by portacaval anastomosis, the hepatic arterial blood flow increases to reach a similar value in all groups. This increment is more evident if previous hepatic arterial blood flow was low, as in normal control rats. Other authors have reported hepatic arterial blood flow increases after portacaval anastomosis in normal rats[10–13] and dogs[14,15]. Also, in cirrhotic patients, portal blood flow deprivation causes an increase in liver arterial blood flow during surgery[16,17]. Lautt demonstrated experimentally that hepatic arterial blood flow does not vary in relation to intrinsic metabolic needs of the liver, but in inverse relation to changes in portal blood flow[18,19], thus acting as a 'buffer'.

The fact that the performance of a portacaval anastomosis in normal and cirrhotic animals leads in 20 days to a decreased liver mass (−30 per cent), while every gram of that mass is less perfused (hepatic total blood flow per unit of mass decreases about 60 per cent and is exclusively arterial), can explain postoperative liver failure, especially if hepatocellular damage was already present. In contrast, hepatic total blood flow and liver mass did not diminish with portacaval anastomosis in portal vein constricted rats, as both were already diminished in the control conditions and portacaval anastomosis in this group gave rise to a minimal loss in hepatic portal perfusion (given that the magnitude of portal–systemic shunting was already 72 per cent before portacaval anastomosis).

As has been pointed out from our longer-term haemodynamic studies in normal rats after portacaval anastomosis, hepatic arterial blood flow per unit of mass (hepatic total blood flow per unit of mass in these circumstances) does not increase ofter the first 20 postoperative days. However, as liver mass increases 2 months after portacaval anastomosis, net hepatic arterial blood flow is actually augmented after the 20th postoperative day. This implies that long-term increases of hepatic arterial blood flow are real and parallel increases in liver mass.

In conclusion, portacaval anastomosis produces after 20 days a limited compensatory increase in hepatic arterial blood flow, that in normal and cirrhotic rats is not enough to preserve liver mass and total blood flow per unit of that mass. In contrast, portacaval anastomosis does not significantly alter liver mass or its perfusion in chronic portal vein constricted rats, as both were previously diminished. Thus, the risk of acute liver failure after portacaval anastomosis is higher in normal rats, and is especially high in cirrhotic animals, as opposed to those with chronic prehepatic portal hypertension. However, some additional recovery of liver mass can be expected with time in portacavally shunted normal rats.

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Case report

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Diffuse cavernous haemangioma of the rectum in childhood

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Diffuse cavernous haemangioma of the rectum is a rare condition which may cause life threatening haemorrhage Adults are mainly affected and there are only sporadic reports of the condition occurring in childhood. We have recently treated two children with rectal haemangiomata in whom diagnostic delay occurred. The purpose of this presentation is to highlight the condition and its radiological features in children. It is hoped that diagnosis will be improved and earlier effective treatment instituted.

Case reports

Case 1

In December 1987 an 11-year-old girl presented with a 2 day history of severe rectal bleeding having suffered minor episodes of bleeding during the preceding 9 months. She had a complicated past history involving numerous operations for multiple congenital malformations (principally oesophageal, cardiopulmonary and spinal). No cause for the bleeding could be found on physical examination. Abdominal radiographs were initially interpreted as being normal Emergency colonoscopy showed an 'inflamed' rectum and sigmoid colon with contact bleeding. Biopsies showed mucosal oedema with an increased number of blood vessels in the submucosa. Review of the abdominal radiographs revealed midline pelvic phleboliths (*Figure 1*) suggestive of a haemangioma. Computed tomographic (CT) scanning showed calcified opacities within a thickened rectal wall and perirectal tissues which enhanced with intravenous contrast confirming the diagnosis of a rectal haemangioma (*Figure 2*).

The rectum and haemangioma were excised and a coloanal anastomosis fashioned using the Swenson technique[1]. Following closure of the covering colostomy there has been no further bleeding during follow-up of 18 months. There was an initial period of faecal incontinence but control has now improved with the child experiencing minor soiling only

Case 2

In November 1988 a 9-year-old girl presented with profuse rectal bleeding On examination the rectal wall felt thickened and granular. Since the age of 3 years she had had numerous hospital admissions for recurrent rectal bleeding, rectal prolapse and diarrhoea. She had undergone repeated colonoscopies, biopsies and radiological examinations with a diagnosis of non-specific colitis. Plain abdominal X-ray showed midline pelvic phleboliths and a CT scan confirmed the diagnosis of a cavernous haemangioma of the rectum Review of the rectal biopsies demonstrated several endothelium-lined, ectatic, vascular spaces in the mucosa, consistent with a haemangioma.

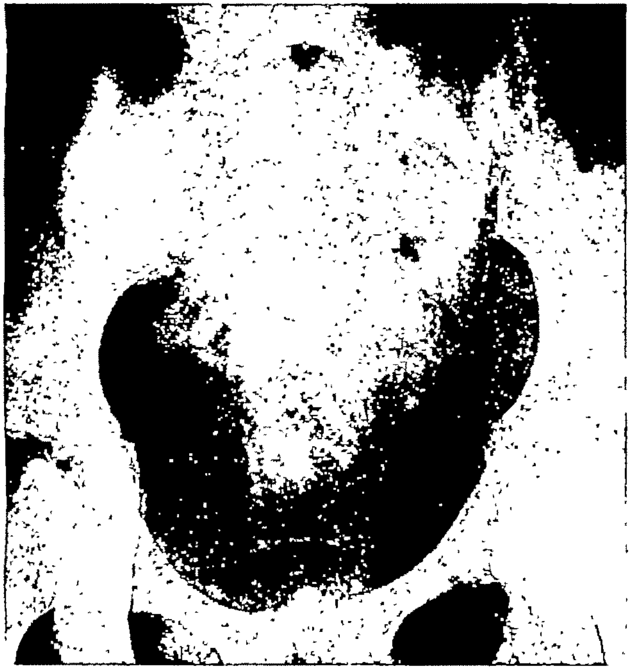

Figure 1 *Plain abdominal X-ray demonstrating multiple, small phleboliths in the midline of the pelvis*

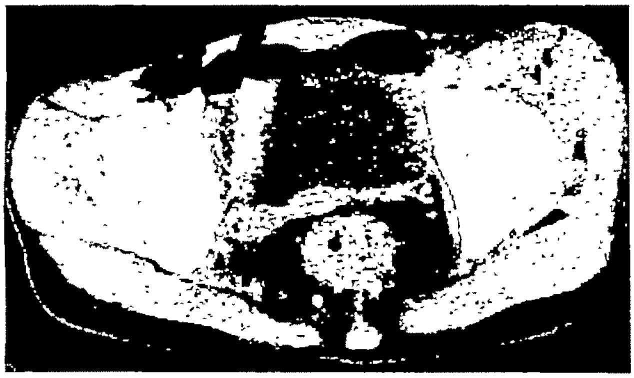

Figure 2 *Computed tomographic scan of the pelvis demonstrating a thickened rectal wall and perirectal tissues with calcified opacities within them*

The lesion was excised and a Swenson procedure carried out with colostomy cover The haemangioma extended to the lower edge of the anal canal and complete excision was not possible. Following closure of the colostomy she suffered two minor episodes of bleeding, neither of which were severe enough to require active treatment Seven months after operation she suffers from marked urgency, leaks faecal fluid and needs to wear a pad, but control is gradually improving.

Discussion

Rectal bleeding is a common problem in childhood and a large number of causes have been identified. Cavernous haemangioma of the rectum is one of the rarer causes of bleeding. The haemorrhage is usually minor, permitting full investigation, but severe, life threatening bleeding can occasionally occur. As the lesion may easily be missed on exploratory laparotomy[2,3], it is desirable for the diagnosis to be established before operation.

There were no distinctive clinical features in our patients, and the radiological, endoscopic and histological findings were not recognized initially. A diagnosis of cavernous haemangioma of the rectum should be considered in all patients with intermittent rectal bleeding who have dilated, endothelium-lined, vascular spaces in the submucosa on biopsy. It would be preferable if the diagnosis could be made without biopsy, as this carries a real risk of serious haemorrhage[3].

The finding of multiple, small phleboliths is a characteristic feature of this condition[3,4]. Pelvic phleboliths are not normally present in children and their presence should alert the clinician to the possibility of a haemangioma CT scanning with intravenous contrast enhancement can provide the definitive diagnosis and obviate the need for biopsy.

We would advocate a sphincter sparing excision of the lesion as the treatment of choice[2,4]. The Soave approach[5] has been recommended[2,4] but this involves submucosal dissection through the haemangioma itself and increases the risk of serious haemorrhage. The Swenson technique seems to be a better option. We accomplished excision of the haemangioma in both cases without difficulty using this technique and, although the patients are not fully continent, control is gradually improving. Coppa *et al*[3] recommended abdominoperineal excision for these lesions, but this would appear to be too radical an approach for most patients.

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Editorial

Are "aberrant nodal gastrinomas" pathogenetically similar to "lateral aberrant thyroid" nodules?

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WHETHER GASTRINOMA TUMORS in paraduodenal lymph nodes are primary tumors, sometimes called "aberrant nodal gastrinomas," or whether they are lymph node metastases from primary duodenal gastrinomas is controversial. There is a corollary situation when this pathogenetic question is compared with earlier concepts of the nature of "lateral aberrant thyroid" nodules Many surgeons will recall the era when the latter were thought to be benign thyroid "rests" but were later generally considered to be metastatic from small differentiated thyroid carcinomas.[1] This understanding came about when surgeons began to excise the ipsilateral thyroid lobe that contained the small "occult" primary lesion. Perhaps the same sequence of conceptual belief can be directed to the possibility that aberrant nodal gastrinomas now represent metastatic lymph nodes from small microgastrinomas of the duodenal wall. Duodenal gastrinomas are now believed to constitute as many as 46% of gastrinomas in the Zollinger-Ellison syndrome[2] Arguments relating to the pathogenesis of "nodal" gastrinomas, primary or metastatic, are presented here for a better understanding of the conflicting viewpoints.

It is tempting to consider so-called extrapancreatic, extragastrointestinal gastrinomas in lymph nodes to be "primary" or "aberrant" gastrinomas because those tumors are often the only tumor(s) that happen to be found during operations for the Zollinger-Ellison syndrome. Fortunately, in the past, their surgical excision usually has been accompanied by resections, such as total gastrectomy or antroduodenectomy. The eugastrinemia that follows such combined operations in a high percentage of cases is probably owing to the possibility that occult primary microgastrinomas of the duodenal submucosa have also been excised, unexpectedly, by the accompanying resection of the duodenum on the gastrectomy specimen, our own experience strongly suggests that this may be true.[3] When we studied 11 patients who had gastrinomas in lymph nodes, seven of them also had submucosal duodenal gastrinomas as primary neuroendocrine neoplasms. These were found by the surgeon or pathologist in the specimens submitted as total gastrectomies or pancreaticoduodenectomies. Six of these seven patients became eugastrinemic; one of the seven had refused a Whipple procedure that may or may not have been curative. Primary lesions were not found in four of the 11 patients with nodal gastrinomas treated by node excision and total gastrectomy, but the early gastroduodenal specimens were not available for restudy. Yet three of these four patients became and remained eugastrinemic over many years postoperatively, hepatic metastases developed in one patient in this group, presumably from an undetected primary pancreatic lesion.

Anecdotal observations in our experience support the contention that nodal gastrinomas are metastatic. When careful pathologic scrutiny is done in a timely fashion, so-called occult primary duodenal lesions have been found. In one patient a yellow submucosal carcinoid-gastrinoma was seen in the base of a duodenal ulcer that had been excised as part of a total gastrectomy for a nodal gastrinoma; long-term eugastrinemia followed this procedure. A patient in whom a nodal gastrinoma was found between the duodenum and the pancreas was treated by a pancreaticoduodenectomy. The surgical specimen, carefully studied because the patient became

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immediately eugastrinemic, disclosed another nodal gastrinoma and a 3 mm primary submucosal gastrinoma of the duodenal wall. She remains eugastrinemic with negative secretin provocation. Another example that suggests a metastatic genesis was observed in another patient, in whom a nodal gastrinoma was excised without accompanying resections. There was no resolution of the hypergastrinemia until a total gastrectomy became necessary (before the advent of acid-secretory receptor antagonists and before our attention was drawn to the submucosal location of duodenal gastrinomas by Oberhelman et al.[4]). The patient then became permanently eugastrinemic.

On the other hand, in support of the idea that aberrant nodal gastrinomas may be isolated primary lesions, there are, to my knowledge, five (possibly six) cases recorded in the literature in which secretin-negative eugastrinemia has followed nodal excision, without gastric, duodenal, or pancreatic resections.[5-9] These few documented observations are seemingly compelling reasons to accept the rare possibility of an entity of primary aberrant nodal gastrinomas; nevertheless, we have already learned that continued long-term surveillance is advisable to detect delayed manifestations of overlooked microgastrinomas.

The idea that duodenal gastrinomas are most likely neurocrinomas (of neuroendocrine cells of the submucosal neural plexus) is circumstantially supported by some interesting observations made by pathologists in the past. A recent translation of the 1869 doctoral thesis by Langerhans[10] reporting the discovery of islet cells discloses. These neural cells are probably the cells of origin of pancreatic VIPomas (and of pancreatic gastrinomas?). Bayliss and Starling,[11] in their description of the discovery of secretin in 1902, attribute Popielski with the observation that there are large collections of ganglion cells in the head of the pancreas that may have contributed to Pawlow's doctrine of neural stimulation of pancreatic secretion. The paper by Barron[12] in 1920, which stimulated the receptive mind of Banting to embark on the work that led to the discovery of insulin, also refers to an abundance of neural tissue among islets In 1928 Masson[13] pertinently described nerve hyperplasia among the endocrine cells of carcinoid tumors. Such cellular associations in intestinal carcinoid tumors were described as "aberrant islands of Langerhans" by Saltekow[14] as early as 1912. Indeed, this process has been called "isletization" of the duodenal wall in cases of the Zollinger-Ellison syndrome. The close functional and cytochemical relationship of endocrine cells of the mucosa with the submucosal neural cells led Pearse[15] to describe the diffuse neuroendocrine system as the third (endocrine) division of the nervous system. It is well known that carcinoid tumors of the duodenal submucosa may secrete peptides, such as gastrin, as well as amines

Until the changing concept of pathogenesis, similar to that of lateral aberrant thyroid nodules, is fully understood, in the management of nodal gastrinomas attention should be directed to the possibility of a primary lesion in the duodenum. As early as 1961, Oberhelman et al.[4] advocated local and radical excision of them. It behooves surgeons, when operating on patients with hypergastrinemia, to carefully palpate by "open duodenotomy" for a possible primary submucosal, not mucosal, lesion; the detection of these small intramural tumors has been reported to be enhanced by the intraoperative use of endoscopic transillumination of the duodenum.[2] The finding of a single submucosal gastrinoma may therefore lead to a simple solution by local excision, as has been advocated.[4, 16, 17] The lesions, however, may be microscopic, so that when a lymph node gastrinoma seems to be the only operative finding or when no tumor is found, a second expedient of an antroduodenectomy may uncover such a microgastrinoma of the duodenum or, alternatively, eliminate antral G-cell hyperplasia as another possible cause of hypergastrinemia in ulcer patients. Finally, a pancreaticoduodenectomy can be reserved as a possible curative procedure for known duodenal gastrinomas that have metastasized to more than one regional lymph node.[17]

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The Vascular Surgical Society of Great Britain and Ireland

Br. J. Surg. 1990, Vol. 77, March, A343–A352

The following abstracts are from the papers presented at a meeting of The Vascular Surgical Society of Great Britain and Ireland, held at Ninewells Hospital and Medical School, Dundee, on 23–24 November 1989. (President: Professor W. F. Walker).

One hundred laser-assisted balloon angioplasties: analysis of failures

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Over the past 30 months, 100 laser angioplasty procedures have been carried out (87 limbs) using energy from a pulsed Nd-YAG laser (wavelength 1064 nm, 100 μs pulses, 10 Hz) delivered through a transparent hemispherical sapphire tip Indications have been restricted to severe symptoms due to a superficial femoral artery (SFA) occlusion which would otherwise require surgical treatment. Analysis of the results shows three main areas in which problems have arisen: firstly, failure of access to the lesion in 25 per cent of procedures (16 per cent of limbs), often due to difficulty in approaching the upper end of an occlusion at or near the origin of the SFA or a large collateral branch; secondly, failure of recanalization in 36 per cent of those with access, although in some of these the energy output was known to be reduced due to technical problems Thirdly, early occlusion (<24 h) in 19 per cent of recanalized vessels, most of which was related to very poor run off in patients with critical ischaemia Late occlusion has not been a problem. four occlusions at 3, 5, 6 and 8 months in 33 patients followed for 6 to 30 (median 12) months. Length of occlusion (mean 16 cm) and calcification have not been considered to be contraindications. Complications have been no greater than those expected for conventional balloon angioplasty, and a 'learning curve' has been demonstrated with successful access and recanalization improving with experience. A new delivery device with an integral balloon catheter has recently begun clinical trials It is hoped that this will solve several of the problems as it is more flexible and provides higher energy densities than the previous device.

Upper limb percutaneous transluminal angioplasty

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Percutaneous balloon angioplasty offers an alternative approach to surgery for the alleviation of ischaemic and neurological symptoms in upper limb arterial occlusive disease We report a series of 27 procedures carried out in 26 patients (26 primary dilatations and 1 repeat dilatation) Thirty-three stenoses and three occlusions were treated with multiple dilatations in four patients There were 23 left subclavian, 10 right subclavian, 1 innominate, and 2 axillary artery lesions

Indications for intervention were: upper limb ischaemia (15 patients) including distal embolism (3), neurological symptoms (10) and combined ischaemic and neurovascular problems (2). Reduced or absent pulses were noted in 24 of the 27 cases. preangioplasty resting brachial systolic pressure was reduced by >10 mmHg in 21 patients, by >30 mmHg in 18, and had a mean value of 50 mmHg

Angioplasty was technically successful in 26 cases In one case a left subclavian artery occlusion could not be traversed. Twenty-five patients were symptomatically relieved at a mean follow-up of 22 (range 2–88) months and had normal pulses One patient developed recurrent symptoms at 30 months and angioplasty was successfully repeated Postangioplasty brachial pressure differentials were <10 mmHg in 21 cases, >30 mmHg in only 3, and had a mean value of 11 mmHg There were 5 complications (18 per cent) associated with the procedure: femoral artery occlusion (1), groin haematoma (2), anginal attack (1), and extension of contralateral stroke (1). Two patients required surgical intervention

Percutaneous transluminal angioplasty was proved a safe, effective, and repeatable alternative to surgical treatment in upper limb vascular disease.

Early results of pulsed dye laser angioplasty with integral ball-tips in long femoral occlusions

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For laser angioplasty to become established as a treatment for occlusive vascular disease of the lower limb it must be effective in the recanalization of long occlusions and establish long-term patency. We have previously reported that a laser wavelength of 480 nm with microsecond pulsing is selective for atheroma and minimizes the risk of thermal damage to the arterial wall[1]. We now report our early clinical experience with this system used with new ball-tipped integral optical fibres.

A total of 25 procedures has been performed in 24 limbs of 22 patients with a mean occlusion length of 24 cm (range 8–49 cm). The patients presented with rest pain (18), severe claudication (4), ulceration (5) and digital gangrene (4). Twenty-two of the procedures (88 per cent) were successful in completely recanalizing the occlusions and the resulting channels were augmented by balloon dilatation. One wall dissection was caused in a vessel occluded from its origin. One recanalization failed because of persistent side-branch entry of the fibre-tip. One perforation occurred, but this did not prevent a successful angioplasty from being achieved. Four early occlusions occurred within 72 h; three of these patients had very poor run-off. The overall clinical success rate was 72 per cent. The resting Doppler pressure index in those successfully recanalized rose significantly from a mean(s.d) of 0·48(0·15) to 0·96(0·16) ($P<0·01$). Over a median follow-up period of 7 (range 1–17) months, there have been two further occlusions, one of which has been successfully retreated with the laser.

These early results in long occlusions treated with this new type of fibre in conjunction with the pulsed dye laser are encouraging Long-term follow-up is awaited.

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Angioplasty: an alternative to surgery for chronic intestinal ischaemia

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Chronic intestinal ischaemia is a difficult clinical problem The diagnosis is often made after exclusion of other causes by demonstrating mesenteric vascular disease by angiography. Until recently the mainstay of treatment has been surgical[1]. Percutaneous angioplasty offers an alternative which may be repeated should symptoms recur. Since 1985, six patients have undergone mesenteric angioplasty The clinical details and results are tabulated

Age	Sex	Angiography	Vessel dilated	Follow-up (weight gain)
63	F	Coeliac stenosis SMA occluded	Coeliac	18 months, asymptomatic (+7·5 kg)
63	F	Coeliac, SMA and IMA stenosis	Coeliac and SMA	8 months, symptoms recurred at 4 months (+2 kg)
69	F	Coeliac and SMA stenosis	Coeliac and SMA	42 months, symptoms recurred at 18 months (+2 kg)
63	M	(Performed on three occasions) Coeliac and IMA stenosis	1 IMA 2 Coeliac and IMA 3 No procedure	7 months, symptoms improved (+7 kg)
46	M	Coeliac and SMA occluded IMA stenosis	IMA	24 months, asymptomatic (+7 kg)
68	M	Coeliac and SMA stenosis	Coeliac and SMA	2 months, symptomatic

SMA, superior mesenteric artery, IMA, inferior mesenteric artery

No significant complications occurred as a result of these procedures. We are currently evaluating the use of duplex scanning for non-invasive diagnosis of mesenteric vascular disease and as part of the objective follow-up of angioplasty

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Results of an 8-year prospective study of internal carotid artery stenosis in asymptomatic patients

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Recent reports of the risk of asymptomatic carotid stenosis have been compromised by either flawed patient selection or the performance of prophylactic carotid endarterectomies during follow-up We report the natural history of a randomly selected group of asymptomatic patients with documented carotid artery disease who were prospectively followed without intervention for up to 8 years. There were 114 men and 74 women. Risk factors included ischaemic heart disease in 17 per cent, diabetes in 10 per cent, hypertension in 46 per cent, and 88 per cent were smokers. The degree of internal carotid artery stenosis was classified by duplex scanning and a total of 259 vessels had evidence of atherosclerosis. Study end-points included transient ischaemic attack (TIA), cerebrovascular accident (CVA) and death. Only one patient was lost to follow-up and no patient underwent endarterectomy prior to developing symptoms. At mean follow-up of four years our findings were as follows:

	Degree of stenosis		
	<50%	50–79%	>80%
n	96	104	59
TIA (%)	1	1	7
CVA (%)	2	4	7
Death (%)	3	6	2

None of the patients suffering a stroke had an antecedent TIA and one patient suffered a fatal stroke. Although ischaemic events (TIA and CVA) are more common in patients with >80 per cent tenosis (Fischer's exact test, $P<0·01$), the incidence of unheralded stroke remains low (2 per cent per year). We conclude that a conservative approach to the management of asymptomatic carotid stenosis should be maintained

Relationship between middle cerebral artery blood flow velocity and mean arterial pressure during carotid endarterectomy

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Certain anaesthetic agents impair or abolish cerebral autoregulation, which has important implications for carotid endarterectomy. Fourteen consecutive patients undergoing carotid endarterectomy underwent peroperative transcranial Doppler monitoring of middle cerebral artery velocity (MCAV) to investigate the relationship between MCAV and mean arterial pressure (MAP) during general anaesthesia.

In the preclamp period, all patients demonstrated a linear relationship between MCAV and MAP (gradient 6.8 cm s^{-1} 10 $mmHg^{-1}$), suggesting impairment of cerebral autoregulation, though carbon dioxide reactivity was preserved. During carotid cross-clamping, the linear relationship was preserved in eight patients, with the axis shifted downwards in four and unchanged in four. In the remaining six patients, there was no increase in MCAV despite an increase in MAP, suggesting inadequate collateral blood supply Shunting however restored the linear relationship in those in whom it was employed. Following final restoration of internal carotid flow, MCAV showed a continuing relationship with MAP in nine patients (gradient 11·97 cm s^{-1} 10 $mmHg^{-1}$), which persisted in three for 12 h after operation

These preliminary data suggest that the volatile anaesthetic agents used in our patients either impaired or abolished cerebral autoregulation and MCAV became pressure passive. While this may not cause problems in the majority of patients, the coupling of MCAV with MAP may have important implications with regard to intraoperative blood pressure management, particularly in those high-risk patients with watershed infarcts or middle cerebral artery stenoses, in whom perfusion reserve may already be impaired There are also implications for blood pressure management in the first 12 h after operation.

Screening for aortic aneurysms and frequency of follow up

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Screening for aortic aneurysms is now being undertaken in many centres Adequate follow-up intervals for those without aortic aneurysm, but with aortic dilation have not been defined We have studied 209 men over 2 years to assess the change in aortic diameter, and we report the influence of hypertension on aortic diameter with time.

The original study group comprised 209 men in the following groups: group 1, 88 normotensive patients; group 2, 87 patients with well controlled hypertension; group 3, 34 patients with severe hypertension requiring hospital admission for control

There were no significant differences in height or weight between the three groups, but group 3 was significantly younger than the other two groups ($P<0·001$ in both cases, Mann–Whitney U test). The aortic diameter was significantly greater in group 3 than in group 1 ($P<0·002$) and group 2 ($P<0·001$). Four patients had aortic diameters >4 cm and were offered surgery.

The results for 132 patients who attended for re-screening were as follows:

	Aortic diameter (mean(s d.); mm)		
Group	1987	1989	Change
1 ($n=60$)	19·23(0·37)	20·12(0·40)	0·88(0·38)
2 ($n=43$)	18·86(0·56)	19·72(0·35)	0·91(0·57)
3 ($n=29$)	22·03(1·31)	22·86(1·75)	0·83(0·85)

The change in aortic diameter was not significant within or between groups (Mann–Whitney U test) In only 1 of 45 patients with an original aortic diameter >2 cm did the diameter increase by >4 cm (a normotensive from 20 to 27 mm). This study suggests that frequent follow-up examinations of patients screened for aortic aneurysm may be unnecessary. Severe hypertension appears to have no influence on this finding.

After the confidential enquiry into perioperative deaths – aortic aneurysm surgery in the Northern Region

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The confidential enquiry into perioperative deaths (CEPOD)[1] suggested an overall mortality rate of 40 per cent for aortic aneurysm surgery in the Northern Region. A 12-month prospective survey was carried out to investigate this, with the co-operation of members of the Vascular Surgical Society in the Northern Region.

Through 1988, data was collected on all patients having elective or emergency aortic aneurysm surgery in the region A total of 198 operations were performed (66 per million population) with an overall mortality rate of 28 per cent (*Table*)

	Number of operations (mortality rate, %)		
	Overall ($n=15$)	Teaching hospitals ($n=3$)	District hospitals ($n=12$)
Total operations	198 (28·3)	88 (28·4)	110 (28·2)
Elective	112 (9·8)	55 (3·6)	57 (15·8)
Emergency	86 (51·2)	33 (66·7)	53 (41·5)

Northern Region hospitals performed 0–42 elective and 1–12 emergency operations per year with mortality rates of 0–26 per cent and 0–100 per cent respectively In the teaching hospitals 12 surgeons performed emergency aneurysm surgery. Four, each operating on >6 elective aneurysms per year had an emergency operative mortality of 50 per cent whereas eight surgeons, operating on 0–6 elective aneurysms per year had an emergency mortality rate of 82 per cent

We conclude that the overall mortality rate for aneurysm surgery in the region (28 per cent) is less than suggested by CEPOD, that there are wide variations in mortality rates for elective and emergency surgery between hospitals, and that the mortality rate for emergency aneurysm surgery in the teaching hospitals was high One correctable factor is that non-designated vascular surgeons or trainees were operating on these patients

1 Buck N, Devlin HB, Lunn JN. The report of a confidential enquiry into perioperative deaths The Nuffield Provincial Hospitals Trust.

Prediction of survival in aortic aneurysm surgery

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A total of 300 vascular surgeons in the UK were requested to supply data for one survivor and one death from an elective or an emergency operation for an abdominal aortic aneurysm Of the first 100 reported cases, 62 (17 emergency, 45 elective) were survivors and 38 (28 emergency, 10 elective) were deaths As yet, 24 per cent of respondents have not reported any deaths, but in the elective group there was an 18·2 per cent death rate. All the patients were Europid; sex and age had no influence on survival. Of emergency patients, 75 per cent were transferred directly to theatre from the accident and emergency department, but the origin of transfer did not influence survival. Consultants performed 91 per cent of elective and 67 per cent of emergency surgery. The mean operating time was 2·8 h in survivors, but 3·9 h in those dying from elective surgery.

Cardiac symptoms were present in 25 per cent of patients and electrocardiogram abnormalities were more common in both emergency and elective deaths than in survivors ($P<0\cdot05$). Serum creatinine levels were higher before and 24 h after operation in those dying than in survivors ($P<0\cdot05$) Minor differences were noted in potassium and white cell count but there were no differences in haemoglobin, sodium chloride, bicarbonate, pH, P_{O_2}, systolic blood pressure, temperature, heart rate or respiratory rate.

In this study cardiac and renal abnormalities were the main predictors of survival.

Thoraco-abdominal aneurysm repair

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The prognosis of untreated thoraco-abdominal aneurysms is poor and only 24 per cent of patients are alive after 2 years We report a consecutive operative series of 39 patients (28 men, 11 women) aged 37–89 years (mean 64 years) treated on our Unit between 1983 and 1989. According to Crawford's classification, 9 patients had type I, 6 type II, 4 type III and 20 type IV aneurysms. Four patients presented with ruptured aneurysms and four had contained leakage, the remaining 31 patients underwent elective repair

Mean theatre time was 273 min (180–420 min) and average visceral ischaemia time was 39 min (range 15–75 min) Blood loss ranged from 1–12 l (mean 4·26 l) and 1–30 units of blood were replaced (mean 11·5 units)

Twenty-two patients had no major complications. Four patients had perioperative myocardial infarction Eleven patients died within 30 days, of whom 4 had either ruptured or had a contained leak Two patients (one of whom died) had postoperative paraplegia. At follow-up (3–60 months, mean 22 months) 23 of the 39 patients were alive and well, although 2 patients had been lost to follow-up.

Our initial experience with this operation has led us to simplify our technique All patients have a Swan–Ganz catheter which is placed after induction of anaesthesia. Heparin is never used and visceral and renal arteries are not occluded.

We suggest that the repair of thoraco-abdominal aneurysms is justified in selected patients and is associated with a better long-term prognosis (59 per cent alive after a mean of 22 months) than conservative therapy

Pulse-Generated Run-off in the assessment of calf vessels prior to femorodistal bypass

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Arteriography is the investigation of choice in patients with critical ischaemia However, it may fail to identify patent distal calf vessels suitable for femorodistal bypass. Pulse Generated Run-off (PGR), a non-invasive method of determining calf vessel and pedal arch patency[1], has been used to assess 110 patients undergoing femorodistal bypass for critical ischaemia The PGR score (0–6) and the arteriogram score (0–6) were analysed with respect to early and late outcome

Successful grafts had a significantly higher PGR and arteriogram score than failed grafts at 1 month ($P<0\cdot001$, Mann–Whitney U test) All successful grafts had a PGR score of ⩾2; in contrast, 17 of the successful grafts had an arteriogram score of <2. Late results are in the *Table*

	PGR score		Arteriogram score	
Year	<2	⩾2	<2	⩾2
GPR (%) 1	14	79	64	87
2	14	64	51	74
		$P<0\cdot001$		$P<0\cdot05$
LSR (%) 1	29	82	71	86
2	29	74	64	79
		$P<0\cdot001$		$P>0\cdot05$

GPR, graft patency rate; LSR, limb salvage rate P values given by the Lee–Desu test

These results confirm the value of PGR in the selection of patients for femorodistal bypass. Patients are now explored on the basis of a PGR ⩾2 even if the arteriogram fails to demonstrate a patent calf vessel.

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Vein collars and patches benefit polytetrafluoroethylene grafts to small vessels

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Despite widespread pessimism associated with the anastomosis of polytetrafluoroethylene (PTFE) to crural vessels, we have attained encouraging patency rates at 1 year by using the Miller collar and Taylor patch anastomotic techniques

We have conducted three experiments *in vitro* (using cadaver internal mammary artery as a crural artery model) which establish the advantages of the Miller collar and Taylor patch over direct PTFE to artery anastomoses.

First, a new method of comparing the circumferential elasticity of normal human saphenous vein, with segments whose length and circumference have been surgically exchanged ($n=9$), has demonstrated the latter to be more 'compliant' ($P=0\cdot02$) This suggests that benefit may be gained by aligning the longitudinal axis of the saphenous vein with that of the arteriotomy – a feature of both vein interposition anastomoses.

Second, we compared maximal pulsatile and constant flow across each type of anastomosis ($n=10$ of each) using a flow model incorporating standard pressure, viscosity, anastomotic angle, and graft and outflow vessel length. Although flow is similar through all three types of anastomosis, this experiment has demonstrated a loss of anastomotic reliability only in direct PTFE to artery anastomoses (i.e. no correlation between flow and vessel diameter; $r=0\cdot04$).

Third, casts of the internal anatomy of the anastomoses ($n=10$ of each) have demonstrated a greater degree of oval distortion of the toe of the outflow vessel of direct PTFE to artery anastomoses than either of the other techniques ($P=0\cdot01$).

This experimental evidence suggests that these vein interposition techniques optimize the mechanical properties of the saphenous vein and protect small arteries from anastomotic distortion These benefits do not occur with direct PTFE to artery anastomoses.

Perioperative graft assessment

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Critics of the *in situ* vein bypass technique suggest that these grafts are likely to require secondary procedures – largely a consequence of retained valve cusps or arteriovenous fistulae. In an attempt to minimize these disadvantages, we have evaluated perioperative graft assessment in 19 consecutive *in situ* vein grafts We have used a non-sterile 8 MHz Doppler probe sheathed in a sterile sleeve and surgical glove. The information provided by the audible Doppler signal and by spectral analysis has been compared To validate our findings, all patients underwent intravenous digital subtraction angiography and duplex graft assessment 6 weeks after operation

The audible Doppler signal enabled detection and localization of persistent fistulae which were then ligated in seven grafts (40 per cent). No persistent arteriovenous fistulae were demonstrated postoperatively. Three (16 per cent) graft stenoses were identified and corrected. One patient required reoperation for a retained valve leaflet which was not detected perioperatively In four (21 per cent), localized changes in peak frequency shift were identified, but these were not considered significant and so far no corresponding stenoses have been identified on follow-up

Spectral analysis did not provide any additional information and as postoperative duplex detected only one (5 per cent) additional technical error, we surmize that its perioperative use is unnecessary.

Audible Doppler is a simple, cheap, effective method of perioperative graft assessment which is available to all vascular surgeons. It is sensitive in the detection of fistulae and could be used routinely for their identification to limit dissection of the vein. Furthermore, it has a sensitivity of 95 per cent in the detection of significant technical errors incurred during *in situ* vein grafting.

Value of anti-platelet therapy following repair of iliacofemoro-popliteal occlusions

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To determine whether anti-platelet therapy is of value following iliacofemoropopliteal vascular surgery in improving immediate and late patency and patient survival, a controlled clinical trial was designed This was a single centre trial, the recruiting of patients was during the years 1971–1975. Of patients, 148 were assigned to the therapy group, receiving 3 × 500 mg acetylsalicylic acid per day, and 150 served as a control group, receiving a placebo and no anti-aggregating medication. The treatment assignment was made using contingency tables according to Ku and Kulback A variety of risk factors (age, sex, height, body weight, diabetic metabolic state, hypertension, history of myocardial infarction, smoking habit, clinical status prior to surgery according to the Fontaine classification, operative technique used and simple angiographic scoring) were in a state of balance The primary end-points were patency and patient survival. Following surgery in the treatment group, 18 reocclusions were seen, whereas in the placebo group 29 occurred ($P<0{\cdot}09$). The probability of function was estimated according to the Kaplan–Meier method, and no statistical significant difference was detected ($P<0{\cdot}192$, Breslow, $P<0771$, Mantel). The last evaluation concerning survival was completed by the end of 1988, yielding a postoperative evaluation period of up to 15 years Data was available for 271 out of the 298 originally recruited patients Not unexpectedly the preoperative clinical status according to the Fontaine classification influenced survival ($P<0001$, Breslow, $P<00001$ Mantel), but neither the presence of ischaemic myocardiopathy ($n=115$) nor treatment with acetylsalicylic acid ($P<0903$, Breslow, $P<0{\cdot}535$, Mantel) altered the probability of survival. In conclusion, acetylsalicylic acid prescribed following iliacofemoropopliteal repair seemed to show an immediate, although statistically insignificant, effect on patency In relation to patient survival, acetylsalicylic acid failed to show any effect, which is at variance with results obtained by others

Duplex-derived volume flow: a comparison of two stress tests in the assessment of 'at risk' femoro-distal grafts

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The identification of failing femoro-distal grafts has been investigated in 40 patients using duplex-derived volume flow measurements, at rest and following reactive hyperaemia. Resting flow was measured at mid-thigh level (mean of 3 readings) Two hyperaemic stress tests (I, an occlusive cuff 50 mmHg above systolic pressure of 2 min, II, active ankle plantar-dorsiflexion for 2 min) were assessed and the results expressed as the mean percentage rise from the resting value +95 per cent confidence interval An intra-arterial digital subtraction arteriogram was performed on each patient and the grafts defined as 'at risk' or control, depending on the presence or absence of graft or run-off stenoses

	Control	At risk
Number of patients	22	18
Mean resting flow (ml/min)	122 + (87–157)	161 + (115–207)
Test I (% rise)	647 + (343–950)	169 + (85–253)**
Test II (% rise)	434 + (51–816)	149 + (60–238)*

* $P<0{\cdot}05$, ** $P<0{\cdot}001$; Mann–Whitney *U* test

There was no significant difference between the resting flow in the control and the 'at risk' groups. There was, however, a significant difference between the two groups following both hyperaemic stress tests. A hyperaemic flow increase of <200 per cent was able to predict 'at risk' grafts with a sensitivity and specificity of 100 and 78 per cent for test I and 53 and 53 per cent for test II respectively.

These results show that, whereas resting flow volumes are similar, the use of a hyperaemic stress test is able to distinguish between control and 'at risk' grafts The 2 min cuff hyperaemic test is simple to apply and is superior to active ankle flexion It may help to identify 'at risk' grafts before they fail

Vascular resistance and prediction of early graft thrombosis

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Run-off is believed to be an important determinant of patency in infra-inguinal bypass grafts We have quantified it by measuring outflow vascular resistance during 67 bypass procedures and assessed its predictive value for early graft thrombosis.

Vascular resistance before and after papaverine vasodilatation was derived from the relationship between pressure and flow while the patient's own blood was infused at 74 ml/min into the outflow artery. Results were expressed in peripheral resistance units (PRU). Graft patency 30 days following surgery was established.

In femoropopliteal grafts proximal to the knee ($n=48$), outflow vascular resistance was a poor predictor of early graft thrombosis. Distal to the knee, vascular resistance after papaverine was significantly greater in six grafts which thrombosed than in 13 grafts which remained patent, with a mean(s.d.) of 869(352) mPRU in the former compared to 576(183) mPRU in the latter ($P<0{\cdot}05$, Mann–Whitney *U* test). In this group, a value of 800 mPRU after papaverine had a sensitivity of 67 per cent, a specificity of 92 per cent and a predictive value of 67 per cent for early graft thrombosis For infracrural grafts ($n=13$), the same discriminant was 80 per cent sensitive, 100 per cent specific and had a predictive value of 100 per cent for early thrombosis

High outflow vascular resistance appears to be an important factor in early graft thrombosis with a potential clinical application as a predictive test.

Skew flap *versus* long posterior flap in below-knee amputation

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Surgeons in 11 centres randomized 191 patients with end-stage critical ischaemia to 98 skew flap (SF) or 93 long posterior flap (LPF) below-knee amputations Techniques including suture materials, drains and stump dressings were standardized within centres but not between centres. Early outcome was compared in respect of 30 day mortality SF 11 (11 per cent) *versus* LPF 16 (17 per cent), primary healing at one week 59 (60 per cent) *versus* 56 (60 per cent); the need for revision at same level (7 *versus* 7 per cent) and the need for revision to a higher level (10 *versus* 7 per cent) There was no statistical difference in early outcome

Postal follow-up revealed that a further 17 (10 per cent) died during the ensuing 6 months. Thus the total mortality which was not statistically significantly different between the two groups was 18 for SF and 26 for LPF. Nineteen were not traced, giving an 88 per cent late follow up. At 6 months, more prostheses had been fitted to SF amputees 59 (88 per cent) than LPF 46 (75 per cent) and more SF amputees also achieved independent walking, 54 (86 per cent) *versus* LPF 43 (70 per cent), but these differences did not reach statistical significance. It is concluded that the skew flap below-knee amputation achieves results comparable to the Burgess operation.

Thrombolysis in acute limb ischaemia: results of a survey of members of the Vascular Surgical Society of Great Britain and Ireland

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A total of 156 vascular surgeons (57 per cent) of the Vascular Surgical Society) responded to a postal questionnaire on the use of thrombolysis in acute limb ischaemia. Over half the respondents had used thrombolysis in the previous 12 months. Low dose intra-arterial streptokinase (89 per cent) was the regimen most frequently used, but 33 per cent had used intravenous streptokinase in the same period. Only 8 per cent had tried intra-arterial tissue plasminogen activator.

The vast majority had treated only a handful of patients. Only four centres had used thrombolysis on more than ten occasions in the previous year. A total of 26 surgeons provided detailed results in 103 patients – limb salvage 60 per cent, amputation 35 per cent and mortality 5 per cent. Minor haemorrhage was the most frequent complication and in many series occurred in up to 50 per cent of patients. Serious haemorrhage requiring blood transfusion and catheter-related complications occurred in fewer than 25 per cent of patients in most series. In the entire survey, there were seven bleeding-related deaths and one from anaphylaxis.

A total of 67 per cent of surgeons with working experience of thrombolysis indicated that selected patients with acute arterial thromboses were most suitable for the technique, particularly if there was no neurological deficit and no run-off for surgical bypass. Distal emboli (46 per cent) and graft occlusions (43 per cent) were regarded as appropriate by some surgeons.

This study demonstrates that a considerable number of vascular surgeons currently use thrombolysis, though sparingly and in selected cases. Patients with acute limb ischaemia should be managed by vascular surgeons who are aware of the new therapeutic alternatives, an ideal supported by over three quarters of respondents to this survey.

Systemic *versus* local peripheral arterial thrombolysis – a randomized trial

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Sixty patients with acute or subacute peripheral arterial thromboses were randomly selected to receive systemic recombinant tissue plasminogen activator (rt-PA) or local intra-arterial (IA) thrombolysis with rt-PA or streptokinase (Sk). The three groups of patients were well matched for age, duration of history, length of occlusion and the presence of neurosensory deficit.

Significantly greater lysis was seen using the intra-arterial route (Sk 80 per cent, $P<0{\cdot}02$, rt-PA 100 per cent, $P<0{\cdot}0001$) compared to systemic rt-PA (45 per cent). The mean(s.d.) overall increase of 0·3(0·1) in ankle–brachial index was similar with systemic rt-PA and IA Sk, but was significantly less than that of 0·56(0·07) achieved with intra-arterial rt-PA ($P<0{\cdot}03$). At 30 days, 9 (45 per cent) patients achieved limb salvage and correction of critical ischaemia following systemic rt-PA compared to 60 per cent (Sk) or 75 per cent (rt-PA) ($P<0{\cdot}05$). Continued patency of the originally occluded vessel after 3 months was significantly lower with systemic than IA rt-PA ($P<0{\cdot}0267$).

Haemorrhagic complications occurred more frequently in the systemic group including one haemorrhagic stroke ($P<0{\cdot}0267$ *versus* (Sk) and $P<0{\cdot}001$ *versus* IA rt-PA). Systemic rt-PA incurred an intermediate effect on systemic activation of the fibrinolytic system between that of intra-arterial Sk and IA rt-PA as shown below. Results are expressed as mean(s.d.)

	Proportion (% original)		
	Systemic rt-PA	IA rt-PA	IA Sk
Fibrinogen	71 (5)	79 (5)	44 (6)*
Plasminogen	68 (5)†	87 (12)†	28 (7)†
α-2-AP	31 (4)	66 (4)*	26 (3)

* $P<0{\cdot}005$ versus other two groups; † $P<0{\cdot}006$ versus all groups

Despite using a fibrin-specific agent (rt-PA), systemic peripheral arterial lysis was associated with reduced efficacy and increased complications. Local low-dose intra-arterial thrombolysis remains the method of choice, with improved and safer lysis being possible using rt-PA.

Reperfusion injury as a triphasic response – a new model

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Inability to salvage an acutely ischaemic limb may be the result of reperfusion injury. A new model demonstrating this has been developed.

In anaesthetized rats a tourniquet producing total ischaemia of one hind limb was released after 6 h in 12 animals (group III) and left *in situ* in 10 rats (group II). Ten control animals had no tourniquet applied (group I). Following tourniquet release, gastrocnemius blood flow was assessed in both hind limbs by intraventricular injection (left ventricle cannulated via right carotid artery) of 15 μm radioactive microspheres (^{46}Sc ^{85}St, ^{141}Ce) 10, 120 and 240 min later. The perfusion indices (study/normal limbs) were compared with similar measurements in animals in groups I and II.

		Perfusion index, median (interquartile range)		
	n	10 min	120 min	240 min
I	10	1·05 (0·68–1·18)	0·97 (0·79–1·13)	1·01 (0·73–1·16)
II	10	0·04 (0·00–0·07)	0·02 (0·01–0·07)	0·03 (0·00–0·07)
III	12	0·12 (0·02–0·43)	0·48 (0·11–0·70)	0·05 (0·01–0·38)

Animals in group III demonstrated low reflow at 10 min (III *versus* II, n.s.; III *versus* I, $P<0{\cdot}01$: Mann–Whitney *U* test) and relative reperfusion at 120 min (III *versus* II, $P<0{\cdot}05$, III *versus* I, $P<0{\cdot}05$). After 240 min reperfusion injury occurred (III *versus* II, n.s., III *versus* I, $P<0{\cdot}01$) with flow less than that during the period of relative reperfusion ($P<0{\cdot}05$).

This undescribed triphasic pattern of blood flow following revascularization reflects the changes that may occur following emergency surgery. Our model provides a method for attempting pharmacological manipulation of low reflow and reperfusion injury.

Rehabilitation of patients after vascular reconstruction for critical limb ischaemia

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Encouraging results following the surgical treatment of patients with advanced lower limb ischaemia have been claimed with respect to graft patency, patient survival and limb salvage. Patients with this condition, however, have a poor life expectancy and little is known about their rehabilitation or any benefit they gain from revascularization of their legs.

In 28 months, 162 patients presented with critical lower limb ischaemia. Revascularization was attempted in 144 achieving a cumulative limb salvage rate of 78 per cent at one year. No patient was lost to follow-up (mean 19, minimum 8 months) and 60 are currently alive with a functioning graft and viable limb. These were matched with primary vascular amputees referred to the regional limb fitting centre who had a prosthetic limb. Rehabilitation was assessed by questionnaire and if necessary home visit, and the groups were compared.

Following reconstruction significantly more patients could walk, leave their home and use public transport ($P<0{\cdot}001$). There were also highly significant differences in the ability to cope with household activities and the incidence of depression, with the reconstruction group faring better.

Vascular reconstruction for critical limb ischaemia currently offers the best chance of rehabilitation and should be undertaken whenever possible

Cost-effectiveness of treating critical ischaemia using quality-adjusted life years

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Rosser has developed the concept of quality-adjusted life years (QALYs), which provides an objective measurement of the cost-effectiveness of procedures[1]. Using this technique, we have compared primary amputation and reconstructive surgery in the treatment of critical limb ischaemia.

The two principal components of quality of life measured by Rosser are physical mobility and freedom from pain. These two factors are scored, according to the Rosser index, on a scale of 0 to 1 A patient with rest pain would score 0, a mobile amputee would score 0 97, and a vascular reconstruction achieving limb salvage would score 0·99.

Using costs quantified in our hospital and making a number of assumptions about operative mortality, rehabilitation rate and graft patency, a spectrum of QALY values has been obtained An unsuccessful amputation (assuming a 20 per cent operative mortality and a chair-bound existence) costs £30 000 per year gained This contrasts with reconstructive surgery in which a successful limb salvage (assuming a 10 per cent operative mortality and a 50 per cent 5-year patency) produces a pain-free mobile patient for £1000 per year gained. For comparison renal transplants and hip replacements cost £4000 and £1000 respectively. Thus, using QALYs, a strong case for aggressive reconstruction can be made. Although the data on which this conclusion is made are crude, we suggest that QALYs are a useful and powerful tool, which should be used to defend the vascular surgeon's resources.

1. Rosser RM, Watts VC The measurement of hospital output *Int J Epid* 1972,1. 361–8.

Effect of shear stress on rapidly formed endothelial cell monolayers on fibronectin-coated polytetrafluoroethylene and gelatin-impregnated Dacron grafts

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The establishment of endothelial cell monolayers not only depends on optimum cell attachment but also on their ability to resist shear stress when a seeded graft is exposed to flow

Endothelial cells labelled with indium-111 oxine were seeded in supraconfluent densities on fibronectin-coated expanded polytetrafluoroethylene (ePTFE) and gelatin-impregnated Dacron® (Gelseal®) graft segments. These grafts, with rapidly formed endothelial cell monolayers, were then exposed to varying shear stresses at flow rates of 200 and 300 ml/min, using tissue culture medium in an artificial flow circuit As the loss of radioactivity represented endothelial cell loss, cell retentions were calculated by the ratio of radioactivity recorded (counts per min) at different time points during 2 h of flow to initial radioactivity

Although initial cell adherence with Gelseal grafts coated with fibrinectin was poor compared to that with ePTFE, once the cells were attached they resisted shear stress of flow better at 200 ml/min and equally well at 300 ml/min (*Table*) Qualitatively scanning electron micrographs of both ePTFE and Gelseal showed patchy coverage of grafts with cells. In ePTFE grafts there was preferential attachment of endothelial cells to the nodes, whereas on Gelseal grafts cells conformed to the knitting pattern of the graft, covering Dacron fibres at different levels and in different directions The cells were also observed to bridge the gaps between individual fibres of the graft.

	ePTFE		Gelseal	
Flow rate (ml/min)	Percentage seeding efficiency	Percentage cell retention	Percentage seeding efficiency	Percentage cell retention
200	74·7 (8·6)	55·4 (12·9)	60·1 (10·8)	69·0 (6·0)
300	70·9 (10·2)	56·5 (15·2)	55·5 (13·0)	66·5 (5·5)

Results are means(s d)

This study shows conclusively that rapidly formed endothelial cell monolayers on ePTFE and Gelseal grafts resisted shear stress of flow equal to that seen in a femoro–popliteal vein graft with significant cell retention at 2 h.

Effect of blood flow on retention of endothelial cells cultured on fibronectin-coated expanded polytetrafluoroethylene vascular grafts

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We have observed improved retention of autologous canine endothelial cells (ACEC) on fibronectin-coated expanded polytetrafluoroethylene (ePTFE) vascular grafts in an *ex vivo* shunt model when the cells were first cultured on the graft surface for 72 h. We report here data on the effect of increasing haemodynamic stress on ACEC retention in the shunt using an identical graft preparation.

ACEC were labelled with indium-111 oxine in monolayer and seeded at $1 \cdot 5 \times 10^5$ cells/cm^2 onto 5 cm lengths of 4 mm internal diameter fibronectin-coated ePTFE grafts Seeded grafts were incubated for 72 h in complete growth medium, then placed in the shunt circuit and perfused for 6 h. Indium-111 activity in the grafts was continuously measured by placing the grafts inside a gamma detection crystal for the duration of the experiment. The grafts were divided into three groups. Group 1 were perfused at 75 ml/min, group 2 at 150 ml/min and group 3 at 225 ml/min Retention of ACEC at each flow rate is shown Data are expressed as the percentage of initial indium-111 activity remaining on the graft at 30 min, 2 h and 6 h after the start of flow.

	Retention of endothelial cells (%)		
Time of flow	Group 1, 75 ml/min	Group 2, 150 ml/min	Group 3, 225 ml/min
30 min	93·8 (1·7)	88·1 (5·0)	83·5 (7·6)
2 h	87·8 (3·2)	84·4 (6·5)	75·1 (8·4)
6 h	82·3 (4·1)	80·2 (7·4)	65·1 (11·8)

Results are presented as mean(s e m.) for four samples

Scanning electron microscopy of control seeded grafts not exposed to flow showed near complete coverage of the graft surface of endothelial cells Grafts perfused at 75 ml/min showed only slightly less coverage which correlates with the loss of radioactivity Grafts perfused at 150 and 225 ml/min showed less complete coverage with groups of endothelial cells rolled up on the graft surface.

In conclusion, while these preliminary results do not show a statistically significant difference after 6 h, they show a trend towards higher loss of endothelial cells with increased flow.

^{99m}Tc-hexamethylpropyleneamineoxime-granulocyte scanning for arterial graft infection

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Arterial graft infection is a serious complication of vascular surgery. Accurate detection is therefore important but current investigations are unreliable This report details the results, in 13 patients with potentially infected grafts, of isotopic scanning with ^{99}Tc^{m}-hexamethylpropyleneamineoxime-labelled granulocytes (HMPAO). There were eight aortic, two axillo–femoral, one ilio–popliteal, and two infra–inguinal grafts, ten were Dacron and three (distal grafts) were polytetrafluoroethylene

Positive microbial cultures were obtained from grafts in seven patients, all with positive HMPAO scans. Positive non-graft cultures were also found in patients with a wound infection, a mycotic aortic aneurysm, and an infected venous cannula, with negative HMPAO scans and no further evidence of graft infection. One patient, whilst on antibiotic treatment, had a negative culture despite a positive Gram stain of pus from the graft. Negative blood cultures were obtained in two patients with negative HMPAO scans who were not surgically explored and had no further evidence of graft infection on follow-up. *Staphylococcus aureus* was implicated in 7 of 11 infections

There were five HMPAO scans negative and eight positive for graft infection including one false positive due to a groin haematoma

(88 per cent specificity) and no false negatives (100 per cent sensitivity) Three of eight patients with proven infection died but the remainder, excluding patients with negative scans, underwent successful removal of the infected graft with revascularization

HMPAO scanning proved a reliable and rapid method of confirming graft infection and may be superior to current alternatives.

Realistic expectations for the patient with intermittent claudication

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Knowledge of both patient and limb prognosis will influence therapeutic decisions in the patient with lower limb ischaemia

Over a mean period of 80 months (range 60–90 months), 112 patients with intermittent claudication were followed Mortality and surgical intervention rates and the influence on these of initial ankle brachial pressure index (ABI), cholesterol, triglycerides and smoking were calculated by life table analysis

Mortality with an initial ABI of $<0{\cdot}5$ was 19, 49 and 67 per cent, and $\geqslant 0{\cdot}5$ was 5, 15 and 23 per cent, at 2, 5 and 7 years respectively No other variable influenced mortality. At follow-up 37 patients were dead and 75 were alive. Myocardial infarction (44 per cent) and cerebrovascular disease (28 per cent) were the common causes of mortality. Cholesterol and triglycerides were not significantly reduced at review and 57 per cent continued smoking The rate of progression to critical ischaemia was 6, 9 and 11 per cent at 2, 5 and 8 years Arterial bypass was performed in eight patients for limb salvage and in seven for claudication. Four extremities were lost, one after bypass and three in diabetics who were non-reconstructable Overall, 66 per cent of survivors were symptomatically stable or improved.

In this study, patients with claudication rarely progressed to critical ischaemia despite failing to reduce their risk factors. ABI predicted which patients were at high risk of mortality. In such patients, a more aggressive approach to ensure compliance with a programme to reduce risk factors rather than emphasis on lower limb reconstruction may improve the natural history

Red cell aggregation and fibrin formation – possible markers for the severity of vascular disease

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Rokitansky proposed in 1852 that fibrin initiates the atheromatous process Recently it has been established that patients with intermittent claudication have higher fibrinogen levels, blood viscosity and haemotocrit compared to controls It is now possible to measure breakdown of fibrin using an enzyme linked immunosorbent assay (ELISA) technique for cross-linked fibrin degradation products (XL-FDPs). XL-FDPs are markers of increased fibrin formation *in vivo* Furthermore, the extent to which red blood cells aggregate under low shear conditions can now be measured photometrically (Myrenne Aggregometer) The mean extent of red blood cell aggregation (MEA) is related to fibrinogen and increased blood viscosity.

We measured these variables in 137 consecutive patients who were assessed clinically by Doppler ultrasound ankle:brachial pressure index and angiography. Results were compared with 200 controls randomly sampled from the general population. Patients with vascular disease had increased levels of XL-FDPs (*Table*) The values of patients with ischaemic rest pain and gangrene were significantly higher than those for patients with intermittent claudication Patients with aneurysm had the highest measured level of XL-FPDs The MEA was increased in patients with vascular disease, again the highest values being in patients with aneurysm, and was associated with fibrinogen level The measured XL-FDPs and MEA correlated with the clinical severity of disease

	Population controls	Claudication	Rest pain/ gangrene	Aneurysm
XL-FDPs (ng/ml)	100	136	280	329
MEA (units)	3·3	4·2	4·2	5·6
Fibrinogen (g/l)	3·00	3·27	4·20	3·80
No. of patients	200	107	22	8

These results suggest that there is an increased tendency for red blood cells to aggregate, and a greater formation and degradation of fibrin, in patients with peripheral arterial disease, and that drug treatment which inhibits fibrin formation (e g. low-dose warfarin) may prevent progression of disease.

Frequency of DNA polymorphisms of the apoprotein B and fibrinogen genes in young patients with peripheral arterial disease

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It is likely that genetic factors contribute, to some degree, to the development of peripheral vascular disease, and this contribution could be expected to be greater in patients presenting with symptomatic arterial disease at an early age We have determined the frequency of DNA polymorphisms of the genes for apolipoprotein B and fibrinogen in 101 patients attending the peripheral arterial disease clinic at Charing Cross Hospital who presented with symptoms of arterial disease before the age of 50. Levels of plasma cholesterol, triglyceride, apolipoprotein B, apolipoprotein A1, lipoprotein (a), fibrinogen and smoking markers were also determined

When results were compared with those from a group of 53 arterial disease-free male controls of similar age and smoking status, the study group had significantly higher mean(s.d.) levels of plasma cholesterol (7·0(1·7) *versus* 5·7(1·2) mmol/l, $P<0{\cdot}001$), apolipoprotein B (0·97(0·27) *versus* 0·88(0·20) g/l, $P<0{\cdot}05$) and fibrinogen (4·41(1·07) *versus* 4·06(0·78) g/l, $P<0{\cdot}05$) The frequency of the apolipoprotein B polymorphisms detected with the restriction enzymes *XbaI* and *EcoRI* was not significantly increased in the study group compared with controls but for the fibrinogen polymorphism detected with the restriction enzyme *TaqI*, an increased frequency (0·38 *versus* 0·26, χ^2 $P<0{\cdot}05$) of the rare allele was seen in the patient group.

The majority of these patients were or still are heavy smokers, which is associated with increased plasma fibrinogen levels. This increase, together with genetic variation at the fibrinogen locus could be contributing to the early development of peripheral arterial disease in these patients

Avoidable deaths in vascular surgery

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The aim was to identify avoidable causes of death in our vascular surgical practice One hundred and fifty consecutive deaths in patients referred for admission to the Vascular Service between 31 October 1984 and 13 July 1988 were analysed prospectively. In the same period there were 2449 admissions and 1796 operations were performed

One hundred and seven patients (71 per cent) were men (median age 73) and 43 were women (median age 82). The primary vascular diagnosis was aneurysmal disease in 71 (47 per cent) and occlusive disease in 75 (51 per cent). Most deaths were unavoidable and 134 (89 per cent) occurred in patients over the age of 65 Thirty four deaths (23 per cent) were considered to have been caused or hastened by errors in management and 21 of these were in the treatment of patients with a ruptured abdominal aortic aneurysm. Avoidable deaths were caused by delayed initial diagnosis (7), interhospital transfer (4), surgical technique (18), anaesthetic error (3), unrecognized postoperative complication (2)

We conclude that errors of surgical technique and diagnostic delay, particularly in patients with ruptured abdominal aortic aneurysm, are the main causes of avoidable death in vascular surgery

Comparison of dipyridamole thallium imaging and clinical indices for the prediction of cardiac risk following vascular surgery

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We compared the predictive accuracy of three clinical indices with intravenous dipyridamole thallium imaging (DP TL) in predicting the cardiac risk of 65 patients undergoing elective vascular surgery

Cardiac complications occurred in 26 patients Analysis identified a Goldman score of <7 and a Detsky score of <10 as the best diagnostic cut-offs, identifying 28 and 26 high risk patients, respectively Eagle's algorithm identified 25 high risk patients and 35 showed redistribution on DP TL. The sensitivity (Sens), specificity (Spec), predictive value (PV), likelihood ratio (LR) and diagnostic accuracy (DA) are shown below.

Test	Sens	Spec	+PV	−PV	+LR	−LR	DA
DP TL	0·88	0·69	0·65	0·90	2·9	0·17	0·77
Goldman	0·56	0·65	0·50	0·70	1·6	0·67	0·46
Detsky	0·23	0·95	0·75	0·65	4·6	0·81	0·66
Eagle	0·57	0·74	0·60	0·27	2·2	0·58	0·68

DP TL had the highest sensitivy and lowest negative likelihood ratio, and out-performed the clinical scales in predicting the cardiac risk of patients undergoing peripheral vascular surgery.

Light reflection rheography: an effective diagnostic test for patients with acute deep vein thrombosis

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The clinical diagnosis of deep vein thrombosis (DVT) is inaccurate in 50 per cent of cases. Non-invasive tests are unreliable, can be complex to perform and remain under-utilized resulting in a high rate of negative venograms.

Light reflection rheography (LRR) is a modification of photoplethysmography and measures the dermal venous blood content. LRR has been shown to correlate well with direct venous pressures[1] but has not been used to detect DVT. One hundred patients with a clinical suspicion of DVT referred for venography were assessed by LRR with standard calf exercise in a sitting or lying position. Results were compared with the findings on subsequent venography assessed independently.

	LRR		
Venogram	Positive	Negative	Total
Positive	42	4	46
Negative	5	49	54
Total	47	53	

The results showed that 54 per cent of venograms were negative confirming a poor clinical diagnostic rate. The sensitivity of LRR in the detection of acute DVT was 91 per cent; the specificity confirmed by a negative X-ray was 93 per cent. The false positives occurred in elderly patients with pre-existing chronic venous disease. False negatives were due to minor partial thrombotic obstruction of an abundant collateral circulation.

LRR offers a simple bedside technique for identifying patients with acute DVT. After screening by LRR, venography can be avoided in a significant proportion of patients with clinically suspected DVT as the negative predictive value is 92 per cent.

1. Nuzzaci G *et al*. Light reflexion rheography: a new method for lower limb venous examination. *Phlebology* 1986; **1**: 231–42.

Postoperative care in abdominal aortic surgery – the first 48 h

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Routine use of the Intensive Care Unit (ICU) varies considerably after abdominal aortic surgery. To assess the need for intensive care, we examined in detail the frequency of medical events and interventions in the first 48 h after aortic reconstruction.

Forty five consecutive patients having elective aortic surgery were studied (36 men, 9 women: age 48–84, median age 66). Twenty nine (64 per cent) had significant preoperative medical conditions. Forty-one were nursed on ICU after operation (median stay 24 h).

Medical events were defined as systolic hypertension ⩾200 mmHg, hypotension ⩽100 mmHg, oliguria ⩽20 ml/h (all from hourly recordings), hypoxia (pO_2⩽8 kPa) or other complications. Medical interventions included prescription of non-routine drugs or intravenous fluids

Thirty six patients (80 per cent) had medical events (hypertension 20, hypotension 17, oliguria 31, hypoxia 10, chest complications 12) and 38 (84 per cent) had medical interventions. Only two had no events or interventions. Twenty seven (60 per cent) had more than one episode of a medical event which would not have been predicted from their preoperative state. There were three deaths (mortality rate 6·7 per cent).

These results support the need for intensive monitoring and experienced medical care after aortic surgery, and invite discussion on where these are best provided.

High dose heparinization does not increase perioperative bleeding

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Although systemic heparinization is used to prevent thrombosis due to stasis, there is no agreed protocol. Lower doses may not provide adequate anti-coagulation in lengthy procedures and higher doses are thought by many to lead to excessive bleeding.

To investigate this effect, 155 consecutive aortic reconstructions were studied prospectively as part of a related project (male:female 3·1; median age 69) Blood loss, wound drainage, transfusion requirement and clinical outcome were recorded. Heparin dosage fell into five groups: none ($n=17$), 0–5000 units ($n=16$), 5–10 000 units ($n=81$), 10–15 000 units ($n=21$), and >15 000 units ($n=20$). The exact amount was determined by the surgeon and anaesthetist according to the clinical circumstances.

Groups were evenly matched for type of operation, duration, and grade of surgeon. Regression analysis revealed no correlation between heparin dosage and operative blood loss ($R^2=0\cdot09$; $P=0\cdot7$), wound drainage ($R^2=0\cdot34$; $P=0\cdot5$), or blood transfused ($R^2=0\cdot15$; $P=0\cdot6$). In addition, there was no significant difference in blood loss between the different heparin protocols ($P<0\cdot05$; Mann–Whitney *U* test). Postoperative thrombotic or haemorrhagic complications were unrelated to heparin dose Less blood was lost with consultants operating (median 1687 ml, interquartile range 1110–2310 ml), than with senior registrars (2249 ml, 1522–3511 ml).

In this study, a high dosage of heparin did not lead to increased bleeding during aortic surgery and surgical technique was confirmed as the most important variable.

Renal artery stenosis – screening by captopril-enhanced diethylenetriamine penta-acetic acid scan

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Renal artery stenosis is the most common curable cause of hypertension but in our experience it is also a common cause of end-stage renal failure in the elderly. Because it is potentially curable by surgery or angioplasty it is important to recognize the condition. However there is no universally accepted screening test Renal vein renin sampling is invasive and is often inconclusive. Angiography remains the gold standard but it is invasive and was associated with myocardial infarction and heart failure in two of our patients. We looked prospectively at 71 patients with renal impairment or hypertension by angiography and captopril-enhanced diethylenetriamine penta-acetic acid (DTPA) screening. The renal angiograms were assessed blindly by an independent radiologist (47 intravenous and 24 intra-arterial digital subtraction angiograms) Stenosis of >50 per cent was present in 24 out of 71 cases (34 per cent). All patients had a carefully monitored captopril-enhanced DTPA scan with no complications. A change in differential function of >4 per cent after captopril was considered a positive result. Two patients were unevaluable due to end-stage renal function (serum creatinine >800 mmol/l).

Angiography	Total number	DTPA +ve	DTPA −ve
Stenosis >50%	23	18	5
Stenosis <50%	46	15	31

Captopril-enhanced DTPA scanning offers a non-invasive screening procedure with 78 per cent sensitivity and 52 per cent specificity in detecting renal artery stenosis of >50 per cent. We recommend this investigation as a useful screening procedure prior to more invasive investigation.

Results of surgical intervention for renal artery disease

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Seventy five patients with renal artery stenosis causing intractable hypertension, with or without renal failure, were treated by surgery or percutaneous transluminal angioplasty (PTA) between 1974 and 1988. The median age was 51 years (range 13–71 years) Of these 48 had hypertension alone and 28 had renal failure with hypertension. Stenosis was caused by atheroma in 50 patients, fibromuscular dysplasia (FMD) in 11, trauma in 3 and the remainder was due to other causes or was unknown Bilateral disease was present in about 50 per cent Nineteen patients underwent PTA, 9 had a nephrectomy and 47 had renal artery reconstruction Renal function, blood pressure and treatment requirements were monitored after operation at 6 months, 1 year and at maximum follow-up.

Overall, the reductions in serum creatinine and blood pressure were most marked soon after operation. Systolic and diastolic pressures were still significantly lower than preoperative values at a median maximum follow-up of 18 months (range 1 week–130 months) but serum creatinine soon rose to pre-operative levels. However some individuals had a striking, persistent improvement in renal function and were able to cease dialysis. Patients aged over 50 were significantly less likely to be 'cured' by intervention (diastolic pressure $\leqslant 90$ mmHg, creatinine $\leqslant 50$ mm/l, no hypertension treatment) ($P \leqslant 0{\cdot}005$), as were those with atheromatous stenosis (*Table*) Although patients undergoing PTA had significantly lower blood pressures and better renal function, their results did not compare well with those of patients undergoing surgery (*Table*).

	Cause			Treatment	
	Atheroma	FMD	Trauma	Surgery	PTA
'Cured' (%)	32	63	100	13	6
Improved (%)	45	37	0	70	76

Patients with renal failure before operation were less likely to have a good result from intervention because of failure to reduce creatinine levels long-term. However the reduction in hypertension was equally effective whether or not there was renal failure.

Assessing the survival of autotransfused red cells in elective aortic surgery using a double isotope labelling technique

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The survival of transfused red cells in the postoperative patient is difficult to measure using a single isotope, as blood loss and fluid replacement dilute the isotope. To overcome this problem, we have used a double isotope labelling technique to measure the effects of cell salvage on the 24 h survival of autologously transfused red cells[1].

Six patients undergoing elective aortic surgery had peroperative autologous blood transfusion using the Solcotrans device A preoperative blood sample was taken and the red cells labelled with ^{111}I A sample of salvaged blood was taken from the reinfusion line and the red cells labelled with ^{51}Cr Both samples of labelled red cells were returned to the patient immediately after operation. Sequential blood samples were taken for isotope counting The ratio of survival of the chromium-labelled salvaged cells to the indium-labelled cells at 24 h indicates if preferential uptake of the salvaged cells by the reticuloendothelial system has occurred. The results were compared with those of four healthy controls. Autotransfusion using this device does not reduce 24 h red cell survival.

	Red cell survival at 24 h			
	Control ($n=4$)		Solcotrans ($n=6$)	
	Median	Range	Median	Range
Indium	86.3 (%)	(78.8–87.5)	73.9	(1.3–84.1)
Chromium	91.3 (%)	(88.4–92.9)	81.5	(1.3–90.2)
Cr/I ratio	1.076	(1.043–1.122)	1.069	(1.000–1.167)

1. Mollison PL. Methods of determining the posttransfusion survival of stored red cells. *Transfusion* 1984; **24** 93–6.

Transthoracic electrocautery as a treatment for palmar and axillary hyperhidrosis

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One hundred and twelve patients with palmar and axillary hyperhidrosis underwent transthoracic electrocautery (TTEC) over a 96-month period All were surveyed by questionnaire asking them to grade carefully their results, and in-patient files were reviewed. Eighty-five patients (76 per cent) replied with a mean follow-up period of 43 months (range 3–95 months). Subjective patient evaluations were made immediately after surgery and after the follow-up interval. These showed that 91·7 per cent reported their condition 'very much' or 'moderately' improved immediately after operation and 84·7 per cent graded it similarly at follow-up. Postoperative morbidity was low Compensatory hyperhidrosis occurred in 64·3 per cent of patients and persisted in 82 per cent of these It was severe in 7 per cent. The cosmetic result was 'moderate' to 'good' in 95·3 per cent. Conforming to the principles of minimally invasive surgery, TTEC should be the treatment of choice in palmar and axillary hyperhidrosis.

Laser vascular anastomosis: preliminary evaluation of a new anastomotic technique

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Laser vascular anastomosis (LVA) is a new technique which employs the thermal effect of absorbed laser energy to achieve fusion of apposed vessel edges. The potential advantages over sutured anastomoses are absence of foreign body reaction, and improved technical ease and speed In a preliminary evaluation, attempted repair of >400 porcine coronary arteriotomies *in vitro*, using either argon or Nd-YAG lasers, was undertaken to establish the optimal technique. Initial mechanical integrity was assessed by measuring bursting pressure (BP) and the degree of anastomotic constriction was determined using a flow rate model Histological examination of selected welds was performed to determine adjacent thermal damage after constant pressure fixation. The tissue temperature profile during welding was also recorded by infrared thermography.

Successful anastomoses (BP>200 mmHg) were achieved in 77 per cent of argon welds but in only 44 per cent of Nd-YAG welds Argon welds were also stronger with a mean(s.e.m.) BP of 249(28) mmHg compared to 164(35) mmHg for Nd-YAG ($P<0{\cdot}05$). Flow rate relative to sutured controls was 69 per cent (argon) and 73 per cent (Nd-YAG) (n.s.) Welding consistently occurred at tissue temperatures >65°C suggesting that collagen denaturation is necessary to achieve fusion. However, histological examination showed significant thermal damage to be confined to the anastomotic line

In conclusion, vascular anastomoses can be produced consistently using laser energy and can withstand suprasystolic pressure. The argon laser is more suited to this technique than the Nd-YAG. A study *in vivo* is currently in progress.

Modification by mannitol of pulmonary oedema after aneurysm surgery

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Abdominal aortic aneurysm repair results in thromboxane generation, a rise in mean pulmonary artery pressure (MPAP) leucopaenia and subsequent non-cardiogenic, permeability pulmonary oedema Animal studies have implicated oxygen-free radicals (OFR) as the initial trigger of this sequence. The aim of this study was to test whether mannitol, a hydroxyl radical scavenger, may inhibit this process.

Patients received mannitol 0·2 g/kg ($n=14$) or saline ($n=12$) intravenously prior to infrarenal aortic clamping With saline, 30 min after clamping, plasma TxB$_2$ levels rose from 124 to 290 pg/ml ($P<0{\cdot}01$), and MPAP from 19 to 27 mmHg ($P<0{\cdot}01$) Aortic clamp release led to further increases in plasma TxB$_2$ to 378 pg/ml ($P<0{\cdot}01$)

and MPAP to 34 mmHg ($P<0{\cdot}01$). The white blood count fell from 9800 to 4400/mm^3 ($P<0{\cdot}01$). Postoperatively all patients were electively ventilated for 12 h. Four to 8 h after surgery, physiological shunt rose from 9 to 20 per cent ($P<0{\cdot}01$) and peak inspiratory pressure (PIP) from 22 to 32 cmH$_2$O ($P<0{\cdot}01$). Chest radiography demonstrated pulmonary oedema while the pulmonary wedge pressure was 12 mmHg, excluding left ventricular failure By 24 h pulmonary oedema resolved, the PIP and arterial oxygen tension returned to baseline Mannitol treatment relative to saline, during and after aortic clamping, reduced. plasma TxB$_2$ levels to 155 and 198 pg/ml ($P<0{\cdot}01$) respectively; MPAP to 21 and 26 mmHg ($P<0{\cdot}01$), minimized the decline in white cell count to 5850/mm^3 ($P<0{\cdot}01$) and the postoperative rise in shunt $\dot{Q}_s/\dot{Q}_t$ to 12 per cent and PIP to 28 cmH$_2$O (both $P<0{\cdot}01$). Chest radiography showed no pulmonary oedema. Finally, studies *in vitro* documented that mannitol 1 to 10^{-4} M, but not dextrose, in a dose-dependent manner inhibited thromboxane synthesis by adenosine diphosphate activated platelets. These data indicate that mannitol maintains pulmonary function following aneurysm repair by limiting ischaemia-induced thromboxane synthesis.

Blood coagulation and rheology in patients with vibration white finger disease

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Vascular surgeons often have to deal with non-surgical vascular conditions. Recently, we have seen a number of patients with fibration white finger disease (VWF), a known cause of secondary Raynaud's syndrome (RS). The pathophysiology of VWF is not yet understood fully. Most hypotheses involve vibration-induced damage to the blood vessel wall In patients with secondary RS caused by connective tissue disorders, e.g. systemic sclerosis (SS), blood coagulation and rheology may be abnormal. We studied these factors in 35 patients with grade III VWF and compared the results to 25 age, sex and smoking matched normal controls and 42 age and smoking matched patients with secondary RS associated with SS as positive controls. Values are expressed as median and range (in parentheses). Compared to normal controls, patients with VWF were found to have less deformable red cells, 1·25 (1·0–2·0) *versus* 1·1 (1·0–1·5) pressure ratio ($P<0{\cdot}05$). Their polymorphonuclear cells produced more leukotriene B4, 26·0 (14·4–39·4) *versus* 17·2 (6·0–38·0) ng/10^6 cells ($P<0{\cdot}05$) Free radical activity was higher in VWF with lower plasma thiol levels than that in normal controls, 450 (417–510) *versus* 480 (418–555) μmol/l ($P<0{\cdot}01$). Platelets were more aggregable to collagen, with a 17 (6–32) *versus* 11 (3–32) per cent change in absorbance reading ($P=0{\cdot}05$). and produced higher levels of B thromboglobulin, 37 (20–55) *versus* 23 (12–41) pg/ml ($P<0{\cdot}01$). Whole blood viscosity at low shear rate was higher in patients with VWF, 20·0 (15·3–26·2) *versus* 17·9 (11·8–20·3) mPa S ($P<0{\cdot}01$). Patients with VWF had a higher fibrinogen titre, 3·1 (2·1–4·8) *versus* 2·6 (2·0–4·0) g/l ($P<0{\cdot}01$), and lower plasminogen activator activity, 68 (45–95) *versus* 106 (64–151) mm^2 ($P<0{\cdot}01$). Factor VIII, von Willebrand factor, and endothelial product were found to be higher in patients with VWF Results from patients with SS were similar to those from VWF patients.

In this study, we have demonstrated that VWF is a true secondary RS with abnormalities in blood clotting and rheology. Although the tests are not sufficiently specific to be used as a diagnosis for this disorder, they may contribute to the decreased blood flow and provide a rationale for the use of anti-thrombotic drugs as treatment for severe VWF.

Correspondence

Gastric cancer: a 25-year review

Sir

We are grateful for the interest in our paper shown by Drs R Jones and J. Rawlinson (*Br J Surg* 1989, **76**: 1099–1100) who draw particular attention to the problem of early diagnosis of gastric cancer. These correspondents criticize our recommendation that early endoscopic assessment be encouraged in patients with dyspepsia as such a policy could produce an unsustainable workload The prevalence of dyspeptic symptoms would indeed preclude such a policy However, in considering such an approach the incidence of new symptoms is more important. Morbidity statistics from general practice[1] report a consultation rate for new cases of gastric cancer of 30 per 100 000 population per year, 420 per 100 000 for gastric and duodenal ulcers and 1140 per 100 000 for disorders of function of the stomach Thus the annual consultation rate for upper gastrointestinal diseases is 1590 per 100 000 Symptoms referable to other sites such as the biliary tract would obviously increase this figure, but would not produce an unsustainable workload for a district general hospital Indeed from our own programme for the early detection of gastric cancer, based on 110 000 patients over 40 years of age[2], we have diagnosed malignancies in 116 of 2939 patients (3 9 per cent) presenting with dyspepsia. Fifty-seven of them had gastric cancer, 19 being limited to the stomach (Stage I and II). Only 24 per cent were macroscopically and histologically normal.

We thus agree that age should be used to select patients, but still advocate endoscopic examination as soon as possible after presentation as the most appropriate method of diagnosing early gastric cancer rather than empirical symptomatic or therapeutic measures which only produce unnecessary delays.

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Essential fatty acids

Sir

The paper by Pritchard *et al*. (*Br J Surg* 1989; **76**: 1069–73) is of some importance as it supports a number of studies implicating various dietary fats in the initiation, progression and treatment of experimental cancers not only of breast but also of the colorectum and pancreas amongst others. Despite this, there appear to be a number of misconceptions culminating in the conclusion that there should be advice to the general population to substantially increase the relative consumption of 'essential fatty acids'.

Essential fatty acids (EFA)

The syndrome of EFA deficiency was first described in rats by Evans, Burr and Burr in 1927 and 1930; it consisted of scaly paws and tails, growth retardation, severe dermatitis, fatty livers, kidney damage, high water intake and reduced life span Hair loss, reduced fertility and an increased respiratory quotient, metabolic rate and skin permeability were subsequently recognized All these effects could be reversed by n–6 fatty acids, in particular those from linoleic acid (18:2, n–6) through to arachidonic acid (20:4, n–6); these are the 'true' EFA (and are all polyunsaturated fatty acids). Whilst α-linoleic acid (18.3, n–3) prevents growth retardation it does *not* prevent skin symptoms. Although n–3 fatty acids are loosely accepted as EFA it is apparent that not all EFA are the same.

Pritchard *et al* state that 'Olive oil which is devoid of essential fatty acids, had no effect on tumour growth'. Yet in Materials and methods we are (correctly) informed that olive oil contains 14 per cent linoleic acid, i e 18.2, n–6 which is *the* classical EFA

This is important as a number of studies have shown this EFA (18 2, n–6), when given as corn oil, has a potent cocarcinogenic effect not only at high levels but also at low levels in experimental breast cancer[1–7], colorectal cancer[8–10] and pancreatic cancer[11] Karmali *et al.*[12] were unable to reduce experimental mammary tumour growth with pure γ-linoleic acid (18:3, n–6) despite so doing with naturally occurring 18:3, n–6 present in evening primrose oil.

δ 6 desaturase

Given the above, the protective role of this enzyme may seem less important The authors do themselves little credit in reporting the human study by Wood *et al.*[13] on reduced red cell stearic acid (18:0 to oleic acid (18 1, n–9) ratios which has been rejected by a number of other studies[14–16] including one of patients with breast cancer[17] Moreover Habib *et al.*[18] would have us believe that they have identified the 'desaturase factor' responsible for converting 18 0 to 18·1, n–9; this would have to be a δ-9 desaturase enzyme rather than deletion of δ-6 desaturase as Pritchard *et al.* indicate.

Whilst the authors emphasize that δ-6 desaturase activity has been found in some transformed and malignant cell lines they take this to mean enzyme *deletion*. An alternative explanation is that certain malignant cell lines have reduced catalase activity[19], which for unspecified reasons is important for δ-6 desaturase activity. Perusal of the authors' own data reveals that comparable desaturation of 18.2, n–6 is occurring in the control, olive oil, primrose oil and fish oil groups, given the different dietary levels of 18.2 n–6 and the preferential substrates for δ-6 desaturase 18:3, n–3 > 18 2, n–6 > 18:1, n–9 > 16 1, n–7.

Finally the cat is not a species renowned for the development of spontaneous cancers; this species lacks δ-6 desaturase.

Human cancer studies

It is surprising that authors fail to mention any previous studies on dietary intervention in human cancer In one, primrose oil failed to show any difference in survival following resection in Dukes' C colorectal cancer[20]; although this was a prospectively randomized trial a negative effect was almost predictable because of low dosage and inadequate numbers In another open study[21] primrose oil produced some 'responses' but lacked the objectivity necessary of a phase II study and again the doses were too low Finally sustained objective responses were observed in two of 12 patients with advanced breast cancer in a phase II study of fish oil supplements[22].

As yet, there is little support for the recommendations of Pritchard *et al* that the general population should eat more 'essential fatty acids' There is no epidemiological data to support such a move. Given the experimental results above this could turn out to be improper advice. Indeed unsaturated fats could be implicated in pancreatic carcinogenesis[23]. The ratio of polyunsaturated to saturated fats in Britain has risen from 0 17 in 1959 to 0 25 in 1981, so has, for example, the incidence of pancreatic cancer. In reaching their conclusion, the Committee on Diet Nutrition and Cancer[24] was careful in advising reduction in total fat consumption and not in addition, altering the balance of fats consumed

There is a growing consensus that carefully conducted phase II and III studies of certain fatty acid supplements are now warranted in certain human cancers. It is important that a balanced view point is given in order to win the confidence of the many clinicians who will be required to participate in these studies.

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Cryotherapy for liver metastases

Sir

I read with interest the paper on 'Cryotherapy for liver metastases: a new approach', by Charnley and colleagues (*Br J Surg* 1989; **76**: 1040–1). It was not clear from their paper how far the zone of necrosis extends beyond the iceball? The suggestion from Zhou *et al.* is that the size of the zone of tissue necrosis produced is comparable to the size of the iceball generated[1]. If this is indeed the case, then it maybe suggested that a 1 cm circumferential rim of liver parenchyma beyond the macroscopic or ultrasonographically defined edge of the tumour should be the minimum encompassed by the iceball. Thus the diameter of the iceball, assuming it is symmetrically generated around the cryoprobe, would be 2 cm and not 1 cm larger than the diameter of the metastasis under treatment as cited by the authors. The rational for this is derived indirectly from the literature on hepatic resection which has shown a high incidence of tumour recurrence if the resection margin is less than 1 cm from the metastasis in the resected specimen[2]. This is presumably from satellite nodules or microscopic deposits located on the periphery of the main tumour mass. Therefore, it would not be unreasonable to expect a significant risk of incomplete tumour eradication as a result of generating an iceball diameter 1 cm greater than the diameter of the metastasis, and thus only allow a 0·5 cm margin of uninvolved parenchyma. This point is of some importance because, unlike alcohol injection and interstitial laser hyperthermia[3,4] which are percutaneous procedures and therefore more easily repeated, cryotherapy requires a laparotomy for its execution. For that reason, it is desirable that each metastasis is dealt with as thoroughly as possible at the initial operation since the need to retreat requires a further laparotomy with its inherent risks.

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Electrocardiographic guided placement of central venous catheters

Sir

Hoffman and colleagues (*Br J Surg* 1989; **76**: 1032–3) describe an ingenious technique of siting the tip of a central venous catheter at the junction of the superior vena cava and the right atrium without using X-rays. However, I would take issue with their suggestion that a different venous route should be chosen if their method of demonstrating *P* wave changes to indicate catheter tip position is unsuccessful after several efforts. By the judicious use of guide-wires and manoeuvres such as hunching the patient's shoulders or using torque to take advantage of the 'memory' in certain catheters which are supplied coiled, it is often possible to correctly place the catheter tip by using X-rays with image intensification. This is the great advantage of using X-ray control and not that X-rays provide hard copy documentation as Hoffman and colleagues mistakenly point out. They should compare the usefulness of their method not with static X-ray pictures, but with image intensification, which is an invaluable aid in the correct siting of the central venous catheter tip, particularly when venous access is limited.

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Book reviews

Vascular Surgery. 3rd ed

H Haimovici. 210 × 280 mm. Pp. 1200 Illustrated. 1989 Hemel Hempstead Appleton and Lange £124.95.

The rapidity of progress in the management of peripheral vascular disease requires constant reappraisal of textbooks on the subject and their frequent revision. This third edition of Haimovici's '*Vascular Surgery*' is published five years after its predecessor It is a five Editor work with contributions from no less than 64 separate authors, only two of whom work outside North America (one in Japan and one in Sweden). Not surprisingly, it has a strong transatlantic bias but, to be fair, areas of controversy are generally highlighted and the reader can use the extensive references to help him judge disputed claims.

This is a major textbook on vascular surgery, a speciality with a proliferation of new developments, and an unashamed multi-Editor and multi-author approach has provided a greater spectrum of expertise and a greater vision of the subject than would otherwise have been possible. Recent developments in vascular imaging, transluminal angioplasty, and laser therapy are well covered as are areas of new understanding, such as the interaction between blood elements and the vessel wall, the metabolic effects of ischaemia (free radicals and scavengers), the relevance of geography to vascular disease, and cerebrovascular syndromes.

While the credentials of the contributors and the contemporaneousness of the text are hardly in doubt, the basic *raison d'être* has not been forgotten. This volume is still a sound practical textbook of vascular surgery with emphasis on standard techniques Its value in this respect is enhanced by the attention given to pitfalls and their avoidance, and to complications and their treatment The whole of vascular surgery is covered in eight sections: basic considerations, exposure of vessels, arterial techniques, occlusive diseases, visceral vessels, thoracic outlet syndromes, venous and lymphatic surgery, and amputations and rehabilitation The book is profusely illustrated with line drawings, angiograms and clinical photographs.

The scope and level of the contents of this volume are aimed at the experienced vascular surgeon and those general surgeons with a major interest in the speciality It is a worthwhile buy for vascular unit libraries The surgeon in training wishing an all inclusive text and atlas of vascular procedures should consider the purchase of this book, it is one of the best available.

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Diseases of the Gastrointestinal Tract and Liver. 2nd ed.

D. J. C Shearman, N D. C Finlayson, D. C Carter 280 × 230 mm Pp 1356. Illustrated Edinburgh Churchill Livingstone. £95 00

'It takes a long time to bring excellence to maturity'.
Publilius Syrus (1st Century BC)

Never before have we seen such a proliferation of scientific fact and such a capacity for its dissemination. There is a plethora of specialist journals and monographs on a whole range of scientific aspects of gastroenterological disease. Whilst necessary, this has imposed a considerable burden on the busy gastroenterologist in trying to assimilate this new knowledge for the patients' benefit Paradoxically the drive towards greater specialization has created a requirement for a general text book of gastroenterology

To be successful such a book needs to be well presented, readable throughout, supported with up-to-date references and to be comprehensive and well indexed. Professor David Shearman from Adelaide and Dr Niall Finlayson from Edinburgh have produced such a text with a simple and uniform style In this second edition, Professor David Carter also from Edinburgh has been introduced as the Surgical Editor I believe that his impact has been considerable; his influence will be appreciated by medical and surgical readers alike.

Despite its size the book handles very comfortably Not only is it informative but it *teaches* in an unobtrusive manner It is greatly endowed with pictures, tables and figures which genuinely illuminate the text I was struck by how recent and pertinent the references were. Important original papers and review articles are highlighted by including them in the section headings.

No doubt part of this success is owed to the inclusion of 14 specialist contributors who cover the following topics endoscopy, tropical medicine, hepatic pathology, paediatrics, radiology, gastrointestinal bleeding, infectious diseases, hepatic tumours, clinical biochemistry, transplantation, stoma care and renal disease. In all, the book contains 49 chapters and covers the whole spectrum of gastroenterology ranging from diseases of the mouth, tongue and salivary glands to anorectal conditions.

This is a modern clinicians' book but those seeking important background biochemistry, physiology and pathology will not be disappointed. This is not just a physicians' textbook I would strongly recommend this book to all surgeons practising in gastroenterology and to those surgeons training in this field.

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Doppler Ultrasound – Physics, Instrumentation and Clinical Applications

D H Evans, W N. McDicken, R. Skidmore, J P Woodcock. 170 × 250 mm. Pp 297 Illustrated. 1989. Chichester· John Wiley and Sons. £47 50

This book is for vascular surgeons and others whose interest is kindled by topics such as the heterogeneity of atherosclerotic plaques, volumetric blood flow measurements and colour flow mapping. There are clear colour images of flow jets and reversals, and up-to-date references, some only a year old. The authors are distinguished medical physicists at the forefront of the spectacular advances in Doppler ultrasound during the last ten years

The interests of the text extend beyond the vascular laboratory, to include cardiac Doppler, fetal heart monitoring, increased blood flow signals in breast and thyroid tumours, and reduced perfusion in renal transplant rejection.

As hospitals take delivery of real-time Doppler imaging systems, with velocities represented as 128 colour shades, turbulence as mosaics, and slow motion action replays, this readable volume will help clinicians and scientists to exploit this exciting new technology.

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Fundamental Anatomy for Operative General Surgery

S J Snooks, R. F. M. Wood. 160 × 235 mm Pp. 91. Illustrated 1989 London Springer-Verlag £12 00

This is a useful book which describes the surgical anatomy for a range of common procedures in general and vascular surgery The text does not aim to be comprehensive but rather gives the anatomical basis without attempting to describe procedures in detail My only criticism is that some of the diagrams are too small for straightforward interpretation.

The book fits easily into the pocket of a white coat and will also be of help to final year students and surgical housemen – in short this is a useful *aide-mémoire* to operative surgery.

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Fundamental Techniques of Plastic Surgery. 8th ed.

I. A. McGregor 245 × 190 mm Pp. 272 Illustrated. 1989 Singapore Churchill Livingstone. £19 50.

My message is 'go out and buy this book, whatever branch of surgery and whatever grade you are as it is inexpensive and you will find it a mine of useful information'. I was surprised to be asked to review it as on the back of the paper back cover it quotes a laudatory review from *The British Journal of Surgery*. On checking I found that this was written by Professor Harold Ellis for the previous edition! It is eight years since the last edition and plastic surgery is changing rapidly so there has been much to update. I was delighted to see that Ian McGregor, who has now retired, is assisted by his son Alan, with a contribution on microsurgery. This modernization has been very satisfactorily completed yet includes the older techniques, such as tube pedicles, as there is still a need for these procedures in single-handed practices or less favourable circumstances yet with daunting reconstructing problems to manage. The book is split into two parts. The first deals with the basic surgical techniques suturing, tissue handling, skin grafts and flaps. The second part deals with surgical applications, particularly in general surgery, orthopaedics and accident work There is an excellent exposition on the problems of management of skin and soft tissue loss with lower limb fractures

The book is clear and easy to read. It is well illustrated with line drawings and photographs, which were all of the highest quality. I have some trivial criticisms, notably the preoccupation with the Zplasty. I have seen some poor results from Zplasty executed by trainees who have read early editions of this book and feel that they may add a Zplasty to every scar excision. It might be helpful in the understanding of a Zplasty if the reader could be instructed to cut out patterns in paper or foam as suggested by Limberg

One other minor criticism pertains to page 48 where an illustration shows a skingraft 'downhill' It is much simpler always to take grafts uphill as the graft does not get in the way I would like to see the mention of stapling and superglue for fixation of skin grafts and would it be possible in future editions to have a list of useful references.

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More of Mould's Medical Anecdotes

R. F Mould. 234 × 156 mm. Pp 284. Illustrated. 1989 Bristol· Adam Hilger. £14.95.

Two hundred and sixty separate items, from one liners to short articles of a few pages, make up this new collection of medical anecdotes. Subjects range from the weird and macabre to the witty and humorous and belong to many centuries, from ancient civilisations to modern society This anthology should entertain both the medical practitioner and the interested layman alike. Its contents will, no doubt, be used to add sparkle to jaded lectures and the medical after dinner speaker might benefit by having it on his shelves.

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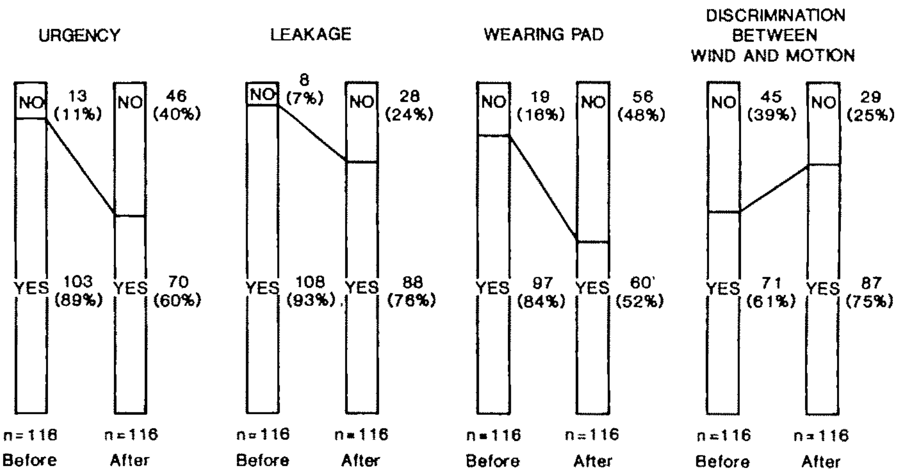
Erratum

'Critical assessment of the quality of continence after postanal repair for faecal incontinence', by K. Yoshioka and M. R B. Keighley, *Br J Surg*; **76**: 1054–1057, Figure 2. The figure which appeared was incorrect. We apologize for this error Figure 2 is presented correctly below:



Quality of continence

Notices and announcements

15–18 March 1990
2nd World Congress of Surgical Endoscopy, Ultrasound and Interventional Techniques
Atlanta, Georgia, USA
Information: Program Committee, SAGES, World Congress on Surgical Endoscopy, Suite 409, 1271 Stoner Ave, Los Angeles, CA 90025, USA

19 March 1990
One Day Symposium on Endoscopic Equipment
London, UK
Information: Mr R A. Miller, Consultant Urologist, Whittington Hospital, St Mary's Wing, Highgate Hill, London N19 5NF, UK

19–29 March 1990
Advances in Neurosurgery
Glasgow & Edinburgh, UK
Information Courses Department, The British Council, 65 Davies St, London W1Y 2AA

28–30 March 1990
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Cardiff, UK
Information: The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

4 April 1990
Colonic Fatty Acids and their Relationship to Bowel Cancer
Newcastle, UK
Information: Department of Surgery, The Medical School, Framlington Place, Newcastle upon Tyne NE4 4HH, UK

1–6 April 1990
Clinical Genetics
Cardiff, UK
Information. British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

2–12 April 1990
The Clinical Medicine of Later Life: the Scientific Basis of Practice
Oxford, UK
Information. The British Council Courses Dept, 65 Davies Street, London W1Y 2AA, UK

19–20 April 1990
General Thoracic Surgery
Las Vegas, USA
Information American College of Chest Physicians, PO Box 93826, Chicago, Illinois 60673, USA

27–28 April 1990
The 3rd International Symposium on Gynaecological Endoscopy
Oxford, UK
Information: Metaphor Conferences & Meetings, 21 Kirklees Close, Farsley, Pudsey, West Yorkshire LS28 5TF, UK

2–4 May 1990
17th Biennial Congress of the Association of Surgeons of South Africa in Bloemfontein
Bloemfontein, South Africa
Information. Dr GF Ferreira, Dept of Surgery, (G72) Univ of the OFS, Box 339, Bloemfontein 9300, Republic of South Africa

9–12 May 1990
3rd International Symposium on Echocardiography and Doppler in Cardiac Surgery
Vienna, Austria
Information. W. Mohl, c/o Interconvention, A-1450 Vienna, Austria, +43/1/23 69/2642

16–18 May 1990
Blood Vessel Imaging Using Ultrasound Techniques
Southampton, UK
Information. Mr K. N. Humphries, Blood Vessel Imaging Course, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

24 May 1990
British Association of Endocrine Surgeons Meeting
London, UK
Information· Mr A W. Goode, Hon Secretary, British Association of Endocrine Surgeons, The London Hospital, London E1 1BB, UK

29 May–1 June 1990
Peripheral Vascular Disease
London, UK
Information: The British Council, Courses Department, 65 Davies St, London W1Y 2AA

5–9 June 1990
European Association for Gastroenterology & Endoscopy: European Digestive Disease Week
Vienna, Austria
Information: Mondial Congress, Faulmanngasse 4/11 A-1040 Wien, Austria

8–9 June 1990
3rd Annual Meeting of The Surgical Infection Society
Antwerp, Belgium
Information: Professor A Hubens, University Dept of Surgery, Stuivenberg General Hospital, Lange Beeldekenstraat 267, B-2008 Antwerp, Belgium

11–14 June 1990
Current Techniques in Hepatic and Gastrointestinal Research
London, UK
Information: Judit Ashton, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN

11–14 June 1990
6th International Congress on Breast Diseases
Boston, Massachusetts, USA
Information 6th International Congress Secretariat, c/o Office of Continuing Education, Tufts University School of Medicine, 136 Harrison Avenue, Box 36, Boston, MA 02111, USA

13–16 June 1990
5th European Symposium on Gastrointestinal Motility
Augsburg, FRG
Information. Professor M Weinbeck, Dept. of Internal Medicine III, Zentralklinikum, D-8900 Augsburg, FRG

20–23 June 1990
Annual Meeting of The Endocrine Society
Atlanta, Georgia, USA
Information· Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

24–28 June 1990
XIII Biennial Meeting of I.S.U.C.R.S.
Graz, Australia
Information Miss D. Strauss, Executive Secretariat, c/o Indru T Khubchandani, 1275 S. Cedar Crest Boulevard, Allentown, PA 18103, USA

24–29 June 1990
The 3rd Oxbridge Organ Transplantation Course
Oxford, UK
Information British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

5–6 July 1990
Surgical Research Society Meeting
Southampton, UK
Information Mr C D Johnson, University Surgical Unit, Centre Block 'F' Level, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK

12–14 July 1990
XVth International Update on Liver Disease
London, UK
Information. Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–15 July 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

15–21 July 1990
1990 Surgical Updating
Milan, Italy
Information Segreteria Organizzativa, MGR, Via Servio Tullio, 4-20123 Milano, Italy

22–27 July 1990
FASEB Summer Research Conference 'Physiology and Pathophysiology of the Sphlanchnic Circulation'
Colorado, USA
Information Federation of American Societies for Experimental Biology, Splanchnic Circulation Conference, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

25–27 July 1990
British Association of Paediatric Surgeons XXXVII Annual International Congress
University of Strathclyde, Glasgow, UK
Information Miss D. Grant, BAPS Administrative Secretary, Royal College of Surgeons, Nicolson Street, Edinburgh EH8 9DW, UK

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong
Information. The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

SURGERY

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Cytoreductive surgery for ovarian carcinoma

Ovarian carcinoma is the most common malignancy of the female genital tract; about 15 in 1000 women will develop this cancer[1]. Early ovarian carcinoma (stages I and II) can be cured by total hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy. Unfortunately, the majority of women with ovarian carcinoma (70 per cent) present with advanced disease beyond the pelvis (stages III and IV)[2]. Cytoreductive surgery or tumour debulking is widely advocated for these patients prior to chemotherapy[2]. Why is this procedure beneficial, what is the extent of the surgery required, and who should be doing it?

The theoretical rationale for cytoreductive surgery is based on the following reasoning[3]. Successful cytoreductive surgery can produce a 'three log kill' of tumour cells, i.e. only 1/1000 of the original neoplastic cell population remains at the end of the procedure. The smaller, better vascularized residual tumour nodules that do remain are more vulnerable to chemotherapy. In addition, reduction in the size of the tumour cell population reduces the chances that the population will produce drug resistant cells by somatic mutation.

Several studies have shown that these theoretical advantages can be translated into improved patient survival after successful cytoreductive surgery. Thus, at one extreme, the worst prognosis is seen among those women with stages III and IV ovarian carcinoma who undergo laparotomy and biopsy only[4]. At the other extreme, regardless of the tumour volume before surgery, reduction in the maximal residual tumour size to less than 15 mm is associated with an improved prognosis[5]. Patients whose residual tumour nodules are less than 5 mm in size after surgery have an even better prognosis[6]. Indeed, cytoreductive surgery that leaves no macroscopic residual tumour is the ideal.

The extent of cytoreductive surgery for ovarian carcinoma, therefore, includes excision of all intra-abdominal disease as far as is practicable and certainly all tumour deposits greater than 15 mm in diameter. Preoperative bowel preparation is an essential prerequisite and a generous midline incision, extending well above the umbilicus, is vital if the procedure is to be done adequately. Complete omentectomy requires visualization and mobilization of both colonic flexures; occasionally colonic resection or even a limited gastric resection is required to remove large cakes of tumour.

A fused tumour mass in the pelvis, that involves the upper rectum, demands retroperitoneal presacral dissection to mobilize the rectum and make the mass accessible for excision. Resection of the tumour mass, uterus, ovaries and the rectum *en bloc* is then performed, followed by a low rectal anastomosis[7]. Therefore, in addition to hysterectomy, salpingo-oophorectomy and omentectomy, a technically demanding intestinal resection may be necessary in up to 40 per cent of patients for adequate debulking of an advanced ovarian cancer[2].

Who should be performing this extensive cytoreductive surgery with minimal patient morbidity rates? It must be a surgeon who regularly performs the necessary surgical techniques, particularly resection and restoration of colorectal continuity. In an ideal world, this would be a suitably trained and experienced gynaecological oncologist but, in the UK, such individuals are presently few and far between. To maximize the chances of a woman with advanced ovarian cancer receiving adequate surgery today, an interested colorectal surgeon must be directly involved in the planning and execution of the operation. For many surgeons such involvement would require an alteration in attitude for them to accept as worthwhile a major intestinal resection that leaves residual peritoneal disease.

Cytoreductive procedures should not be embarked upon by junior surgeons managing an acute complication of ovarian cancer. This is of particular importance because some 25 per cent of ovarian cancer patients present to non-gynaecologists. In such circumstances, inexperienced surgeons are best advised to confine themselves to tumour biopsy and the relief of the urgent problem. Definitive surgery should be performed shortly thereafter, followed by chemotherapy. By contrast, to give the

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patient chemotherapy and postpone surgery until some remote future date is of no benefit[8]. A joint surgical approach to advanced ovarian carcinoma, in a suitably prepared patient and an elective and unhurried setting, offers the best hope of beneficial cytoreductive surgery. If no joint approach can be provided locally, the patient with advanced ovarian cancer should be referred to a unit which has developed the necessary surgical expertize.

Successful debulking of an ovarian carcinoma requires the combination of a certain philosophy and certain surgical skills; a philosophy that demands removal of all major tumour deposits and the surgical skills to carry out difficult colorectal resections. Until circumstances allow widespread access to adequately trained gynaecological oncologists, women with advanced ovarian carcinoma would be best served by the involvement of interested colorectal surgeons prepared to provide the skills needed for radical debulking and prepared to accept the philosophy of cytoreductive surgery.

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Br. J. Surg. 1990, Vol. 77, May, 483–484

Aetiology of venous ulceration

Ulceration of the skin of the lower limb has been an affliction of the human race since the time of Hippocrates. It is almost certainly the price we pay for having emerged from the ocean and learnt to stand erect. The presence of the 'calf muscle pump' has made this possible by maintaining venous return against the force of gravity but, when this mechanism fails, persistently elevated venous pressure on exercise causes ankle oedema, lipodermatosclerosis and, eventually, cutaneous ulceration.

The calf pump can fail because of defective muscle action, which is occasionally seen in patients after poliomyelitis or, more commonly, in those with severe arthritis of the ankles, knee or hips that restricts muscle action. The cause of calf pump failure is however usually in the veins themselves. This may occur in the superficial veins as a result of primary venous dilatation with secondary valvular incompetence (varicose veins) or in the deep veins because of constriction, luminal obliteration and valvular destruction following thombosis (the post-thrombotic limb). Congenital venous valvular aplasia is an extremely rare cause of venous malfunction accounting for a tiny proportion of all patients presenting with venous ulceration.

The relative proportions of the two main causes of venous malfunction (varicose veins and post-thrombotic limb) in patients with ulceration are disputed and may vary in different countries, in different areas of the same country and even in different hospitals in the same city, depending upon the referral practice. We have recently reviewed the ascending and descending phlebograms of a large cohort of patients attending the St Thomas' Hospital ulcer clinic with venous ulceration confirmed by abnormal calf function studies carried out after ulcer healing. Between 40 and 50 per cent of the ulcerated limbs had changes in their deep veins, which were consistent with a previous thrombosis[1].

It is still not known exactly how failure of the calf pump leads to ulceration. The old concept of 'stasis' was dealt a body-blow by the consistent finding of a raised oxygen tension in the venous blood of ulcerated limbs. The metabolic studies of Hopkins *et al.*[2] showed that lipodermatosclerotic skin and ulcerated tissues have a more than fivefold increase in blood flow and a significantly reduced oxygen extraction when compared to normal 'control' calf tissues. This does not refute the idea of arteriovenous shunts causing ulceration although no evidence of such shunts was found in the isotope studies of Partsch and his colleagues[3].

Pericapillary fibrin has been found in the dermis of almost all patients with the preulcerative condition of lipodermatosclerosis (pigmentation, inflammation and induration of the gaiter skin). It has been suggested that the interstitial accumulation of fibrin and other macromolecules resulting from the perisistently elevated venous pressure causes a diffusion block to the passage of oxygen and other nutrients to the skin[4]. Fibrin cuffs have recently been demonstrated in the skin surrounding venous ulcers[5]. The fibrin cuff hypothesis fits comfortably with the work of Hopkins and his colleagues, but this type of physiological study cannot of course confirm that fibrin is responsible for the apparent diffusion block. Fibrin sheets have however been shown to reduce oxygen diffusion in water bath experiments.

Leach and Browse[6] showed that raising the venous pressure in the hind limb of an animal model caused greater quantities of fibrinogen and inhibitors of tissue plasminogen activator to enter the lymph and raising the renal venous pressure has been shown to cause a similar rise in the constituents of renal lymph[7].

Recently Thomas *et al.*[8] have found that significantly more white cells 'disappear' from the venous blood in the dependent limbs of patients with 'chronic venous insufficiency' than disappear from the dependent blood of normal limbs. They have suggested that these vanishing leucocytes are being 'trapped' in the capillaries beneath venous ulcers where they cause capillary occlusion and tissue ischaemia. Coleridge Smith *et al.*[9] provided some support for this hypothesis by finding that the number of cutaneous capillary 'tufts' within a specified area of the calf skin was also reduced by dependency in patients with chronic venous disease, the observation appearing to indicate that the capillary tufts were being occluded. They were unfortunately only able to examine normal rather than lipodermatosclerotic skin with their technique of capillary microscopy. This concept of localized tissue ischaemia resulting from white cell capillary occlusion is at variance with the findings of Hopkins *et al.* although their patients were only examined with their limbs in the horizontal position. It is now important for the 'white cell supporters club' to show that leucocytes are being trapped in the skin of patients with lipodermatosclerosis and ulceration. It would be nice to know if this phenomenon occurs before the cutaneous changes are present at this might provide some indication that it is a cause rather than an effect.

Pericapillary fibrin deposition has been shown to precede the development of lipodermatosclerosis[10]. Biopsies were taken from the apparently healthy normal limbs (with no evidence of lipodermatosclerosis or previous ulceration) of patients with unilateral ulceration. These so called 'normal' limbs have been found to be far from normal when they are examined critically and must be considered at high risk of developing ulcers[11]. Fibrin cuffing was found around the dermal capillaries in all of these high

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risk limbs. In contrast it was not found in the calf skin of normal limbs nor was it found in limbs with uncomplicated varicose veins or in the thigh skin of the same high risk limbs. A scoring system was devised which related the number of capillaries found to have perivascular fibrin cuffs per high power field to the total number of capillaries on cross-section (stained with laminin). The fibrin score correlated with the cutaneous $P_{\mathrm{tcO_2}}$ as measured by a transcutaneous oxygen electrode (Spearman rank correlation coefficient $= 0{\cdot}62$, $P < 0{\cdot}01$). The greater the number of capillaries with fibrin cuffs, the lower the level of transcutaneous oxygen. This implies that as fibrin deposition occurs around more capillaries so tissue anoxia increases.

Gajraj and Browse[12] have recently shown that artificial radioactive labelled fibrin 'clots' formed beneath the gaiter skin lyse more slowly in limbs with lipodermatosclerosis than under healthy calf skin. The fibrinolytic system appears to be depressed, but this seems to be a local phenomenon within the calf tissues rather than an overall reduction in systematic fibrinolysis. Cutaneous tissue plasminogen activator levels and radioactive fibrin clot lysis times[13] were reduced when venous hypertension was deliberately induced. However the model of venous hypertension used received criticism because it relied on a proximal arteriovenous fistula which almost certainly reduced distal limb perfusion; tissue ischaemia has not been shown to reduce tissue plasminogen activator levels in a corresponding fashion. It would therefore appear that fibrin deposition is encouraged by the reduced levels of tissue plasminogen activator which might result from raised venous pressure. Others have previously found that tissue fibrinolytic activity is lower in the calf veins than in groin veins.

What can we conclude from these studies? There certainly seems to be good evidence that a raised venous pressure is associated with pericapillary fibrin deposition, and this almost certainly coincides with a local reduction in tissue plasminogen activators (and perhaps even a rise in the level of their inhibitors, although this requires further proof). Fibrin deposition has been shown to precede the development of skin changes in limbs that can be considered to be at high risk of developing ulceration. It has not of course been shown that fibrin causes venous ulceration and, although there is a suggestion that reversal of this process may be beneficial, it has certainly not been proven beyond doubt. Further studies are essential to elicit the mechanisms of ulcer development, because a better understanding of causation will almost certainly lead to improved prospects for prevention.

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Acute management of spinal cord injury

The value of specialized, regional units for rehabilitation of patients with spinal cord injury was first established in Great Britain in the 1940s by Guttmann[1] at Stoke Mandeville and since then confirmed in many other countries. Slower to materialize has been the development of such regionalized, specialist units for the acute care of patients with acute spinal cord injury (ASCI). Some experts such as Bucy[2] in the United States have advocated the development of a system of care for ASCI patients which includes their transfer to an Acute Spinal Cord Injury Unit (ASCIU) within 2 h of trauma. In large countries such as Canada or Australia, it would be impossible to comply consistently with this rule, even with an air ambulance system. In Canada, the argument for the concentration of care of ASCI patients in the acute phase was cogently made by Botterell *et al.*[3] on the basis of a study of all such patients injured in the province of Ontario during 1969 and 1970. They found numerous deficiencies in terms of the evacuation, transport and dispersion of these patients among a multitude of acute care institutions, and they argued for a system of care which involved early transfer to a small number of organized, multidisciplinary ASCIUs, each treating a sufficiently large number of patients to achieve proficiency. In Canada, the first ASCIU was opened in 1974, and sufficient time has passed to allow evaluation of the concept of the ASCIU, especially in the light of new information about the pathophysiology and treatment of ASCI.

In Canada, there is demographic evidence that there has been a significant reduction in the proportion of patients with complete ASCI, i.e. an injury causing complete loss of voluntary motor and sensory function below the level of the injury. Whereas in previous years approximately 65 per cent of ASCIs were complete, the current figure is approximately 45 per cent[4]. This decline is mainly due to improved management, including better first aid, evacuation, and transportation, and improved treatment in specialized, regional units[4–6]. Other demographic evidence of improvement derives from the reduction in the mortality rate[4,6], rates of complications[6,7] and costs of care[7,8] achieved by specialty units. Thus, there is good evidence that these improvements, so well demonstrated several decades ago by the followers of Guttmann who advocated an organized, regionalized, multidisciplinary approach to the rehabilitation of patients with ASCI, also accrue from the same approach applied during the acute phase.

What is the pathophysiological substrate accounting for the improved results? It is well known that the spinal cord is rarely completely transected in patients with ASCI and that some patients with major incomplete injuries have shown substantial neurological recovery[4,9,10]. In the laboratory, various models have shown that substantial recovery of spinal cord function can occur spontaneously but, more importantly, that recovery can be enhanced by a variety of experimental treatments[11,12]. There is now good evidence that 'all is not lost' with the initial primary or mechanical injury and that, subsequently, the spinal cord undergoes additional biochemical and pathological damage known as the secondary injury, and that the the secondary injury is amenable to treatment. The exact nature of the secondary injury is unknown and may include one or more of the following postulated mechanisms: post-traumatic ischaemia, continuing compression, oedema, damage by excess release of free radicals, arachidonate or excitatory amino acids, and electrolyte imbalance with intracellular accumulation of calcium and extracellular accumulation of potassium ions.

The post-traumatic ischaemia mechanism has much experimental support. For example, in our laboratory we have shown that major ASCI produces severe ischaemia of the injured segment and that the ischaemia can be ameliorated by a variety of agents including a calcium channel blocker[13]. If the ischaemia is not relieved promptly the end result is spinal cord infarction which markedly reduces the chance of neurological recovery because of the inherent low capacity of central axons to regenerate, although there is now ample experimental evidence that central axons can regenerate in the spinal cord[11,12]. Unfortunately there is currently no reliable means of promoting axonal regeneration in patients with ASCI. Thus, clinical management must aim at reducing the secondary injury which, in my view, provides great opportunity to help these patients. The concept of the secondary injury places great responsibility on all health care workers providing care to an ASCI patient during the first few hours after injury. The 'ABCs' of management (airway, breathing

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and circulation) which apply to victims of all types of trauma and are designed to support the life of the victim have a more specific connotation for the victim of spinal cord trauma because attention to the ABCs will support the spinal cord itself by supporting the microcirculation of the cord. Indeed, initial management of ASCI patients may be complicated by the specific haemodynamic and respiratory alterations caused by the cord injury itself. For example, the more cephalad and severe the cord injury, the more profound the neurogenic shock manifested by systemic hypotension and bradycardia. Similarly, respiratory embarrassment may range from diaphragmatic breathing and paradoxical respiration to complete apnoea. Thus, specific regard for the ABCs of trauma management will not only ensure the survival of the spinal cord injured victim, but will also aid the survival of the cord by reducing the ravages of post-traumatic ischaemia and infarction.

Management of the acute phase also requires judicious selection from among the multitude of new operative and non-operative methods of treating the injured spinal cord and spinal column, including halo devices, instrumentation for internal fixation, and various surgical approaches for accomplishing varying combinations of reduction, decompression and fusion. Although there is still no firm evidence that surgical treatment is superior to other means, it is now established that spinal surgery can be performed safely in selected patients with ASCI[14]. However, there is strong experimental evidence that decompression is effective in the acute stage for specific injuries[15].

In conclusion, the acute management of spinal cord injury is one of the most difficult tasks facing the first aider, emergency physician, surgeon and specialist dealing with paraplegia. Much can be done to aid the survival of the patient and the injured cord. A multidisciplinary, team approach such as offered by a regional ASCIU offers major advantages for improved, cost-effective care.

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Gut barrier function and the surgeon

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There is accumulating evidence that multiple organ failure is not always the result of an established septic focus. Increasing attention has centred on the gut as a reservoir of bacteria (and bacterial endotoxins) that can traverse the intestinal mucosal barrier (a process called 'bacterial translocation') and initiate the septic state. Although the link between haemorrhagic shock and sepsis was recognized decades ago, the full experimental demonstration of this phenomenon is more recent. It was shown to occur in three main settings: physical disruption of the gut mucosa, impaired defence mechanisms and altered gut microbial ecology. Conditions such as haemorrhagic shock, burns, protein malnutrition and sepsis are seen in the severely ill surgical patient or the multiply injured, and are known to cause various combinations of circumstances favourable to bacterial translocation and endotoxin absorption. These may play an important role in the mortality of the critically ill.

Keywords: Bacterial translocation, endotoxin absorption, intestinal mucosa

The association of sepsis, usually in the form of an occult intra-abdominal focus, and remote organ failure is well recognized[1] However, in a large proportion of patients dying of multiple organ failure, no septic source can be found either clinically or at autopsy[2–4]. Attention has been focused increasingly on the role of the gastrointestinal tract as a reservoir of pathogens that can enter the circulation by crossing the gut mucosal barrier, initiate the septic process and perpetuate multiple organ failure.

The passage of viable bacteria from the gastrointestinal tract, through the epithelial mucosa, to other sites such as mesenteric lymph nodes, liver, spleen, peritoneal cavity, lymph and the blood stream is termed 'bacterial translocation'. Equally important may be the passage of bacterial endotoxins through this barrier Bacterial translocation or endotoxin absorption take place under a great number of conditions, notably haemorrhagic shock, thermal injury, malnutrition, sepsis and jaundice.

In the absence of a well-established theory, the purpose of this review is to collect together the somewhat fragmentary evidence that links incompetence of the gut mucosal barrier to sepsis and multiple organ failure. Our purpose is to evaluate the evidence incriminating the gut as a source of pathogens, review the functional and histological disturbances of the gut mucosa, examine the conditions under which bacteria and toxins can cross this barrier and report on some of the clinical implications of interest to the surgeon.

The gut as a source of pathogens

Jacob Fine is held to be the first author to have extensively investigated the link between the lethality of traumatic shock and the gut origin of systemic endotoxaemia. In his shock model, the gut was indeed the source of endotoxins and invasive Gram-negative bacteria; there was failure of the reticuloendothelial system to detoxify these enteric endotoxins and the irreversibility of haemorrhagic shock was attributed to a breakdown of bacterial defence mechanisms[5–8].

It is now well established that the gastrointestinal tract acts as a source of pathogens in the granulocytopenic patient[9]. There is accumulating evidence that this is also the case in a variety of other circumstances, especially in the critically ill surgical patient. After reviewing a large series of surgical patients with systemic candidiasis, Stone *et al.*[10] have demonstrated experimentally the ability of intestinal *Candida* to cross the gut mucosa and reach first the portal venous system and then the systemic circulation. They have successfully applied their findings to the prophylaxis of *Candida* infection in a large series of patients with burns.

Fry *et al.*[11] could find no primary source of bacteraemia in 75 per cent of patients suffering from 'non-histotoxic' clostridial infection and this led them to speculate that these organisms migrated across an altered gut mucosa. Incompetence of the hepatic reticuloendothelial system may have been an additional contributing factor. Kreger *et al.*[12] noted that 30 per cent of patients with Gram-negative bacteraemia have an undefined primary focus of sepsis Similarly, in a review of 123 episodes of enterococcal bacteraemia[13], no primary focus could be found in as many as 42 per cent of cases, despite extensive diagnostic bacteriological studies, exploratory laparotomies and autopsies. A study of 205 critically ill patients has incriminated the proximal gastrointestinal tract as an occult reservoir of pathogens responsible for intensive care unit-acquired infections[14] *Staphylococcus epidermidis*, *Candida* and *Pseudomonas* were the most frequent microbial isolates and it was significant that these organisms were those most frequently cultured from gastric and jejunal secretions In at least five patients, the organism was isolated from the proximal gut well before it had caused an invasive infection In a murine model, colonization of experimental intra-abdominal abscesses by enteric organisms was demonstrated; the most commonly found species were *enterococci*, *Escherichia coli* and *staphylococci*[15].

Low-flow states as a cause of intestinal mucosal disruption and loss of barrier function

Under normal circumstances, the intestinal mucosa permits only the selective passage of nutrients into the circulation, while maintaining a protective barrier against the absorption of various intraluminal particles and substances, including bacteria and their toxins. The impermeability of the cellular membranes and the tight junctions between the mucosal cells

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play an essential role in this function. Low-flow states have been shown to cause the disruption of the gut mucosal barrier[16]. Most experiments have used animal models of haemorrhagic shock to investigate this phenomenon

Sloughing of intestinal mucosal cells and decreased mucus production, together with increased permeability to curare, have been observed in shocked dogs[17] Lysosomal rupture may render the mucosa more vulnerable to digestive enzymes[18]. The luminal presence of pancreatic elastase, trypsin and chymotrypsin appears to contribute significantly to the loss of the physiological barrier function in the ischaemic gut[19] In another model of haemorrhagic shock[20], the increased permeability to horseradish peroxidase (a macromolecular histochemical tracer) suggests disruption of the specialized junctional apparatus connecting the mucosal cells. The irreversibility of haemorrhagic shock can be prevented by adequate preservation of intestinal blood flow[21,22], while perfusion of the gut lumen with oxygen and nutrients may protect against the mucosal damage caused by splanchnic ischaemia[23].

The histological changes in the gut mucosa caused by a decrease in splanchnic blood flow have been studied in the canine model by Chiu *et al.*[24]. Not only was the histological sequence of mucosal damage consistent and reproducible, but its degree was a function of the severity and duration of visceral ischaemia The early microscopic lesion consisted of a subepithelial space (Gruenhagen's space) starting at the apex of the villus and progressing down its sides, resulting in the lifting of the epithelial layer from the lamina propria. Eventually, disintegration of the lamina propria, haemorrhage, ulceration and transmural necrosis may occur. Similar morphological changes were demonstrated in shocked rats[25]; in addition, bacteria were clearly seen crossing the caecal mucosa on some of the histological sections Disruption of the mucosal membrane allows invasion of the portal circulation by luminal bacteria and their toxins, proteins, digestive enzymes, gut hormones and products of necrotic tissue[26]. Intestinal mucosal lesions caused by shock were studied in humans[27] on ante-mortem specimens, and were found to be identical with those previously described in the dog by Chiu *et al.*[24]. The suggested pathogenic process at work in a hypoxic villus in the face of almost unchanged villous blood flow is a short-circuiting of oxygen in the intestinal countercurrent exchanger at the villous base and in the deeper layers of the mucosa[27].

Hypoxia *per se* has been held to be the key factor causing the ischaemic mucosal lesion. There has been, however, recent evidence[28] to suggest that reperfusion after an episode of intestinal ischaemia releases oxygen free radicals responsible for increasing the severity of the mucosal lesion. The oxygen free (or superoxide) radical, a cytotoxic form of molecular oxygen, is generated by the enzyme xanthine oxidase. In a feline model of intestinal ischaemia[28], allopurinol (a specific inhibitor of xanthine oxidase) or superoxide dismutase (a scavenger of oxygen free radicals), have been shown to protect the intestinal mucosa from the effects of hypoperfusion Similar conclusions were drawn from the study of the effects of reperfusion of the ischaemic murine gastric[29] and intestinal[30] mucosa.

As intestinal mucosal pH is a reflection of mucosal oxygenation, the detection of intramucosal acidosis in the gut, by a simple tonometric method[31], may have some clinical value in the early diagnosis of splanchnic ischaemia in the critically ill.

Bacterial translocation and endotoxin absorption

Haemorrhagic shock

Bacterial translocation, associated in some cases with endotoxin absorption, has been demonstrated in several models of haemorrhagic shock. Baker *et al.*[25] used a rat model subjected to haemorrhagic shock of variable duration (30, 60 or 90 min) and were able to culture bacteria (especially *E. coli* and *Enterococcus*) from the mesenteric lymph nodes, liver, spleen and blood. Rats subjected to 90 min of shock showed the highest incidence and degree of translocation, and the highest mortality rate at 24 h; no difference in the caecal bacterial population levels between control and shocked animals was noted In a different murine model of severe haemorrhagic shock subsequently treated with fluid replacement[32], bacterial invasion of the portal and systemic circulation was demonstrated throughout the post-shock period. The majority of the rats died relatively late (more than 24 h) after recovery from the initial hypovolaemic insult The same group of authors further tested the hypothesis that the bacteria were of enteric origin by feeding their rats with isotope-labelled *E. coli*[33], finding a correlation between plasma assay activity and postshock mortality. The link between haemorrhagic shock and sepsis was then investigated in a small number of patients admitted to a trauma unit with a low blood pressure and without injury to a hollow viscus[34]. The highest incidences of significant endotoxin levels and positive blood cultures were found in the group of patients with the lowest systolic blood pressure on admission (systolic blood pressure below 80 mmHg).

Injury to the intestinal mucosa is a direct consequence of haemorrhagic shock. It results in the failure of the mucosa to act as an efficient barrier to the indigenous enteric bacteria. However, it is possible that other effects of haemorrhagic shock may contribute to the propensity of the bacteria to cross this barrier. Haemorrhagic shock results in complex phenomena responsible for a disruption of host immunity. Impaired host immune response is sufficient in itself to promote bacterial translocation[35–37], and the inflammatory response is known to be depressed in shocked animals[38]. Furthermore, severe haemorrhagic shock decreases the acute inflammatory peritoneal response to bacteria and inhibits their clearance from the blood[39]; it is associated with impaired leucocyte function[40] and humoral immunity[41].

Thermal injury

Sepsis is a major complication of burns Although contamination of burn wounds by exogenous organisms or by endogenous organisms originating from the upper or lower gastrointestinal tract is accepted as the main mechanism of infection, the role of bacterial translocation is being evaluated[42]. Howerton and Kolmen[43] studied rats colonized with fluorescein-labelled bacteria (*Pseudomonas aeruginosa*) by gastric intubation and subjected to third-degree thermal injury. They demonstrated that unburned rats failed to develop a bacteraemia while in the burned rats there was an immediate bacteraemia and bactichylia of 7 h duration; intact, viable, labelled *Pseudomonas* organisms were found in the intestinal wall and the mesenteric lymph nodes. Furthermore, in non-surviving burned rats, the organism was found in the burned area within 90 h, and in distant lymph nodes and organs at the time of death.

The influence on bacterial translocation of the disruption of the intestinal flora of burned animals by colonization with pathogenic organisms or by the use of antibiotics has also been assessed. It has been known for some time that translocation occurs when the ecology of the indigenous gastrointestinal flora is disrupted by allowing bacterial overgrowth[44,45] Enteric Gram-negative bacilli are found in the mesenteric lymph nodes of mice given various antibiotics in their drinking water for a few days[46]. Abnormal gastrointestinal tract bacterial colonization due to antibiotics together with immunosuppresive drug therapy synergistically promoted translocation that resulted in lethal sepsis[47].

The interference with the intestinal flora in the setting of thermal injury was studied in a mouse burn model. Specific pathogen-free mice, derived from germ-free mice, were used[48]. These animals harbour a stable enteric bacterial flora and, when they are subjected to burns, no translocation occurs. However, after antibiotic decontamination and colonization with *E. coli*, the incidence of bacterial translocation and the numbers of *E. coli* found in the mesenteric lymph nodes, spleen, liver, blood and peritoneal cavity increased with increasing burn area. In a slightly different model[49], the same authors studied the pattern of organ involvement by the translocated bacteria. No translocation occurred after a 20 per cent body surface area burn, while after a 40 per cent burn, the bacteria translocated to the mesenteric lymph nodes but did not spread to other organs. After antibiotic decontamination and colonization by *E. coli*, a 40 per cent burn was responsible for the involvement of distant organs by translocated *E. coli*. The highest incidence and degree of translocation to distant sites was demonstrated in *E. coli*-infected rats subjected to a 40 per cent burn and given a small oral dose of penicillin sufficient to allow *E. coli* overgrowth.

Translocation is known to occur if the host is immunosuppressed and T cell-mediated immunity, as well as other host defence mechanisms, was found to be important in preventing translocation in burned mice[50]. The effect of burns on the intestinal mucosa is not fully understood Burns could lead to severe hypovolaemia that could account for bacterial translocation even in the absence of antibiotic therapy. In addition, it has been shown that thermal injury decreases the small bowel mucosal and pancreatic weights in burned rats Interestingly, the subcutaneous or intraperitoneal administration of bombesin restored gut mucosal and pancreatic weights to normal and significantly reduced bacterial translocation[51].

Nutrition

The effects of nutrition on the intestinal barrier function have been considered from two points of view, namely the relationship between malnutrition and bacterial translocation and the comparative influence of parenteral and enteral nutrition on this phenomenon. One might expect that translocation may be facilitated by nutritional deficiencies as malnutrition can impair host immune defences[52] and disrupt the normal microecology of the gastrointestinal tract[53]. Moreover, the physical integrity of the gut mucosa depends on an adequate nutritional state, starvation in the rat was followed by an excessive small bowel weight loss and a reduced proliferation of the intestinal epithelial cells[54]. Deitch *et al.* demonstrated that malnutrition alone[55] or in combination with thermal injury[56] did not promote bacterial translocation in the mouse. Whereas the intraperitoneal or intramuscular administration of endotoxin was followed by bacterial translocation from the gut to the mesenteric lymph nodes[57], the combination of protein malnutrition with endotoxaemia was associated with translocation to systemic organs[55] This experiment is supported by the observation that endotoxin alters gastrointestinal mucosal integrity[58].

There are various mechanisms which might account for the adverse effects of parenteral nutrition on the gut barrier function. Mucosal atrophy occurs after prolonged periods of parenteral feeding[59] Glutamine is a specific nutrient used by the gut. Because it is unstable, it is absent in commonly used parenteral solutions and, during parenteral nutrition, the enterocyte is supported by the conversion of valine to glutamine. In enteral feeding, glutamine may be present in insufficient amounts, but it can be derived from a large number of amino acids. When a glutamine-enriched solution was used, a significant increase in intestinal mucosal cellularity occurred[60]. Mucosal atrophy caused by the delayed institution of enteral nutrition may have served as a stimulus for the hypercatabolic state in burned guinea pigs[61]. A similar effect may take place in burn patients[62]. One clinical study[63], however, showed that the route of nutrition administration did not affect the incidence of postseptic multiple organ failure and the mortality rate. Delayed institution of enteral feeding after the start of the hypermetabolic response may be an explanation for this failure to demonstrate the superiority of the enteral route.

In addition to the physical disruption of the intestinal mucosa, parenteral nutrition causes a marked reduction in the amount of S-IgA (intestinal secretory immunoglobulin A) which plays a major role in preventing attachment of luminal bacteria to the mucosal cells[64]. In a comparative study of rats fed parenterally with rats fed orally with the same solution, translocation to regional nodes was significantly greater in the rats fed intravenously. A decrease in the luminal S-IgA levels was associated with greater degrees of translocation[65] In the human, parenteral feeding (compared with enteral feeding) was found to have an adverse effect on neutrophil function, possibly weakening intestinal defence barriers[66].

Sepsis

The presence of sepsis itself may promote bacterial translocation, establishing a positive feedback loop where an abnormal gut permeability may perpetuate or even amplify the septic state. Experimental intra-abdominal abscesses induce bacterial translocation[15]. Endotoxin administered to rats, intramuscularly or intraperitoneally, is responsible for the colonization of mesenteric lymph nodes by enteric bacteria[57]. In man, the increased intestinal permeability to mannitol and lactulose after a brief exposure to endotoxin[67] is consistent with the experimental observations.

Intra-abdominal pathology

Experimental intra-abdominal abscesses are colonized by gut bacteria even in the absence of spillage of intestinal contents[15,68,69]. Peritonitis in the rat[70] results in massive proliferation of *E. coli* in the intestinal lumen and this, in turn, leads to bacterial translocation and endotoxin absorption; the resulting endotoxaemia produces immunosuppression as evidenced by the impairment of delayed-type hypersensitivity responses. Simple intestinal obstruction in man causes bacterial translocation. The culture of mesenteric lymph nodes obtained at laparotomy in patients suffering from intestinal obstruction (without bowel necrosis) showed an incidence of bacterial colonization of 59 per cent in contrast to an incidence of 4 per cent in patients operated on for other reasons[71].

A large amount of research has centred on the role played by enteric endotoxins in the pathogenesis of postoperative renal failure complicating obstructive jaundice. An extensive recent review deals with this topic[72]. Bile acids prevent the absorption of endotoxins by degrading the endotoxin molecules[73,74]. Endotoxaemia is the result of both the absence of bile salts from the intestinal lumen and dysfunction of the reticulo-endothelial system[75]. It causes renal vasoconstriction and redistribution of the intrarenal blood flow away from the cortex[76], and constitutes an important factor in the pathogenesis of acute tubular necrosis. There is recent evidence to suggest that the tumour necrosis factor (a macrophage product) mediates the effects of endotoxins in the experimental animal, causing haemorrhagic lesions in the gastrointestinal tract, renal tubular necrosis and pulmonary changes similar to those of the adult respiratory distress syndrome[77].

Mechanism of translocation

The migration of bacteria across the intestinal mucosa occurs in a great variety of circumstances. It seems to be promoted by any combination of three settings, namely physical disruption of the gut mucosa (e.g. due to hypovolaemic shock), decreased host immune defences (as caused by agencies such as severe trauma, malnutrition and immunosuppressive drugs) and interference with the gut ecology (e.g. as a consequence of wide-spectrum antibiotic therapy) with resulting bacterial overgrowth. The actual mechanism of translocation remains unknown and little work has been devoted to its elucidation. Wells *et al.*[78] have hypothesized that intestinal bacteria are ingested by macrophages, transported to an extraintestinal site and then liberated from the dead cells; the degree of translocation was greatly decreased in macrophage defective mice which had been decontaminated and colonized with *E coli*. It is not known whether other routes of migration are used by the translocating organisms.

Clinical implications

Therapeutic strategies intended to minimize the deleterious effect of endotoxaemia have shown some promise, at least in obstructive jaundice. Although there was no beneficial effect on renal function derived from the perioperative administration of polymyxin B[79], the preoperative administration of bile salts to jaundiced patients decreased portal and systemic endotoxaemia, and met with encouraging success in the prevention of renal dysfunction[80,81].

In spite of a large body of evidence documenting the important role of bacterial translocation in explaining the development of sepsis in the laboratory animal, the evidence remains circumstantial in man. It is, however, well established that the gut acts as a source of endogenous contamination in the critically ill surgical patient and, in particular, in the severely injured. Recent clinical research has concentrated on decreasing the risk of endogenous infection by greatly reducing the number of enteric aerobic Gram-negative bacilli and yeasts. In this process, the normally predominant anaerobic flora is retained as a protection against colonization or overgrowth with drug-resistant strains (this phenomenon has been termed 'colonization resistance'[82]). Although the case for the use of such selective decontamination of the digestive tract is not yet established[83–87], its results in traumatized patients are encouraging. Using this approach, Stoutenbeek *et al.*[83,84] report that the total infection rate was reduced from 81 per cent to 16 per cent.

Border *et al.*[88] have studied a large series of patients with severe blunt multiple trauma. They showed a positive correlation between septic severity score and two variables, namely the duration of mechanical ventilation and the duration of antibiotic treatment. In addition, a correlation was found between an absence or decrease in the incidence of sepsis and the institution of an enteral protein diet. The hypothesis that the need for prolonged ventilation, antibiotic therapy and parenteral nutrition reflects the presence of more severe disease is refuted by the authors. They argue (on somewhat tenuous grounds) that the septic state, largely the result of endogenous contamination by enteric bacteria, is the consequence, not the cause, of these three methods of management.

Incomplete treatment on admission results in repeated operations and prolonged ventilator dependency. This in turn may delay the enteral institution of nutrition and the situation may be aggravated by the enforced supine position (aptly referred to as the 'horizontal crucifixion position')[88,89]. Intestinal bacterial overgrowth is promoted by wide-spectrum antibiotics and the perpetuation, by the supine position, of gastric and colonic stasis. The gut mucosal barrier is rendered incompetent by the initial hypovolaemic shock and the absence of enteral nutrition. The combination of these factors is responsible for the initiation of the septic state, often around the tenth day in the intensive care unit, an event which has come to be considered as almost the norm. A plea is made for early, agressive and complete management of the multiply injured patient (including operative treatment of fractures)[88,89] if the incidence of late post-traumatic mortality is to be reduced.

It must be emphasized that, at least in the clinical setting, there is as yet no definite proof that sepsis of gut origin is an important cause of multiple organ failure This hypothesis merits serious consideration on the strength of rather convincing laboratory experiments. Other avenues equally deserve to be explored. Some have produced evidence to support the view that multiple organ failure is the result of severe generalized inflammation, without sepsis, caused by activated inflammatory mediators and tissue anoxia[3,90] Others do not exclude the possibility that the primary trigger is the failure of the immune system which leads to organ failure and associated sepsis[91]. In any case, these theories do not exclude the participation of enteric bacteria and endotoxins in the chain of events that results in multiple organ failure.

The link between haemorrhagic shock and sepsis was established a few decades ago. Histopathological as well as bacteriological evidence have been adduced in support of this theory A large amount of experimental work has provided the proof that enteric bacteria and their toxins can translocate, under abnormal conditions, across the intestinal mucosa, even in the absence of any demonstrable physical disruption of this natural barrier Only recently has the gut come to be considered as the 'motor of multiple organ failure'[4]. There is, at present, more than a suspicion that bacterial translocation and endotoxin absorption play an important role in the development of sepsis and its resulting mortality in the severely injured or the critically ill surgical patient.

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Review

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Male homosexuality, HIV infection and colorectal surgery

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The sexual practices of male homosexuals may lead to the development of a wide variety of colorectal and perianal diseases. This review describes the pathogenesis of these conditions, their management, and the influence of HIV infection on these conditions.

Keywords: Homosexual, rectum, anus, HIV, immunodeficiency

It has been estimated that the anorectum is an organ of sexual fulfilment for 2·5 million of the population in the UK[1] In view of this observation, it is hardly surprising that colorectal and perianal diseases have become a major problem in male homosexuals. Although the 'gay bowel syndrome'[2–4] was originally coined to describe colorectal and anal symptoms in homosexual men, this term is misleading as it implies a single disease entity. It is now recognized that male homosexuals are at risk of developing one or more of a heterogeneous group of colorectal or perianal diseases[5] which can be conveniently classified into: (1) infective enterocolitides; (2) non-condylomatous perianal diseases; (3) anal condylomata, and (4) anorectal malignancies.

Male homosexuals constitute one of the major risk groups for the development of the acquired immunodeficiency syndrome (AIDS) in the Western world[6,7]. Recently it has been suggested that up to 30 per cent of these patients acquire colorectal or perianal diseases and that more than half of these may require surgical treatment[8]. Moreover, the advent of this disease has broadened the spectrum of gastrointestinal diseases in homosexual men.

It seems likely therefore that colorectal surgeons will become increasingly involved in the diagnosis and management of colonic and anorectal problems in male homosexuals The purpose of the present review is twofold; firstly to outline the clinical presentation, diagnosis and management of colorectal and perianal diseases in male homosexuals and secondly to highlight the influence of human immunodeficiency virus (HIV) infection on the types of disease and treatment.

Classification of HIV infection

Infection by HIV may be acute or chronic Acute infection is usually subclinical but may be characterized by a mononucleosis-like syndrome. Seroconversion does not occur in all individuals infected (the virus is generally less infective than the hepatitis B virus). In those individuals who do seroconvert, this is likely to occur in most cases within 6 weeks of infection[9]. Classification of chronic HIV infection and AIDS has been confused by the many and varied terms used by different authors. In an effort to rationalize this situation, the classification suggested by the Centers for Disease Control (CDC)[10] has been widely adopted and distinguishes between those patients who are asymptomatic HIV antibody positive and those with manifestations of immunodeficiency

The CDC classification divides patients with HIV infection into four groups. Group 1 are patients with acute HIV infection, while group 2 are asymptomatic HIV antibody positive individuals. Group 3 are HIV antibody positive patients with persistent generalized lymphadenopathy. Group 4 are HIV antibody positive patients with the AIDS related complex, opportunistic infections, neurological disorders or tumours.

Colorectal and perianal diseases in HIV negative homosexual men

Infective enterocolitides

The sexual activities of homosexual men such as anoreceptive intercourse and oroanal contact expose the colorectum to infection from a wide variety of sexually transmissible organisms[11–15]. In practice, the exact mode of presentation depends on the nature of the infecting organism[16] and on the degree and extent of inflammation. Proctitis is a common manifestation with symptoms which do not differ from those due to other causes[17]. *Neisseria gonorrhoeae* remains the most commonly isolated pathogen, usually producing a mild proctitis with loss of mucosal vascular architecture, oedema and contact bleeding in the distal 10 cm of the rectum[11,16,18]. Less commonly, primary syphilitic infection and herpes simplex virus can involve the rectum only and give rise to the symptoms of a mild proctitis[11]. By contrast, infection by lymphogranuloma serotypes of *Chlamydia trachomatis* produces the symptoms of severe proctitis with granulomatous inflammation and extensive ulceration of the rectum, inguinal lymphadenopathy and constitutional symptoms[5,11,16,19,20]. In those infections due to enteric pathogens such as *Salmonella*, *Shigella* and *Campylobacter* species, *Giardia lamblia* and *Entamoeba histolytica*, where the pathological changes extend into more proximal colon, the symptoms of proctocolitis predominate and include constitutional disturbance, fever, abdominal pain and bloody diarrhoea[5,12,14–17].

Clinical evaluation should include taking a careful history of sexual proclivity and an assessment of risk factors for associated HIV infection[21]. All patients should have sigmoidoscopy and rectal biopsy in addition to stool microscopy, culture and serological tests for syphilis, gonorrhoea and hepatitis. Barium enema examination and colonoscopy may be helpful in assessing the proximal limit of the disease.

In HIV antibody negative patients, these enterocolitides respond to appropriate antimicrobial chemotherapy based on the results of culture and sensitivity Full resolution of symptoms may be anticipated.

Perianal diseases

Symptoms due to perianal disease such as pruritus ani, bleeding, pain, discharge and occasionally faecal incontinence constitute the other main reason for male homosexuals seeking the advice of a coloproctologist. Trauma to the anus, such as major disruption of the anal sphincter mechanism, is not a common presenting complaint, but occasionally follows 'fisting' or the insertion of foreign bodies into the anal canal[5,22,23]. The more common types of perianal disease encountered in homosexual men fall into two main categories, namely non-condylomatous lesions and condylomata acuminata.

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Non-condylomatous perianal lesions

Some perianal lesions may be caused by infections[24]. For example, the herpes simplex virus can cause multiple perianal ulcers, and painful chancres may be the presenting feature of primary syphilitic infection[2,3,5,11,16].

The spectrum of non-condylomatous perianal diseases in the homosexual population has been examined by several authors. Sim reviewed 251 anorectal procedures carried out on heterosexual and homosexual patients with abscesses, fistulae, fissures, haemorrhoids and skin tags and demonstrated no differences in the types and prevalence of perianal lesions between the two groups[25]. By contrast, others have shown that the prevalence of anorectal sepsis such as abscess and fistula is statistically significantly higher in male homosexuals when compared with heterosexual men[26]. Chronic intersphincteric abscess or fistula seems to be particularly common in male homosexuals[5,25,26] The reason for the high incidence of anorectal sepsis is unclear but may be related to repeated local trauma as the result of anoreceptive anal intercourse and other homosexual practices Although fissures do not appear to be more prevalent in homosexual men than in the heterosexual population, they may be multiple and situated in unusual positions in the anal canal[5,26]. The occurrence of atypically situated anal fissures and chronic anal ulcers in these patients may also be related to repeated local trauma. Other lesions such as skin tags and haemorrhoids are, in the authors' experience, seldom the sole cause of perianal symptoms in male homosexuals and are almost always associated with other perianal problems[26]. In patients who are HIV negative, these perianal lesions should be treated in the usual way[8,26].

Condylomata acuminata

Anal condylomata are seen in over 50 per cent of 'healthy' homosexual men and have been reported to be seven times more common than penile condylomata[4,27–29]. In recent years it has been established that genital condylomata are a sexually transmissible infection caused by human papillomavirus[30,31]. Of over 60 different types of human papillomavirus only four are commonly sexually transmissible[32]. These virus types are associated with a spectrum of lesions ranging from benign anogenital condylomata (human papillomavirus types 6 and 11) to invasive anal and genital cancers (human papillomavirus types 16 and 18)[33–35]. The natural history of condylomata in the immunologically normal host is not completely understood. Successful eradication of these lesions by scissor excision, diathermy or laser vaporization may be equally successful[36,37]. Whichever treatment method is selected, recurrent condylomata occur in about 15 per cent of patients, probably due to a reservoir of subclinical infection[38].

Anorectal malignancy

At present there is little evidence to suggest that anorectal malignancy is more common in HIV negative male homosexuals than in the heterosexual population

The influence of HIV infection on the types of lesion and outcome

Gastrointestinal infection in HIV positive patients

Patients with HIV infection present special problems to the clinician involved in the diagnosis and management of gut infections in male homosexuals. The common venereal and enteric pathogens such as the herpes simplex virus, and *Salmonella* species pursue a more severe clinical course and are more refractory to treatment than similar infections in HIV negative homosexuals[6,22,39,40]. The depression of cellular immunity which accompanies HIV infection predisposes patients to the risk of opportunistic protozoal and viral infections which have a predilection for the gastrointestinal tract. *Cryptosporidium* is probably the commonest protozoal cause of diarrhoea which may affect up to 30 per cent of patients with symptomatic HIV infection[41]. This parasite produces intermittent or persistent diarrhoea, abdominal colic, and fluid and electrolyte loss. In severe cases it presents with protracted watery diarrhoea of several months' duration, weight loss and malabsorption *Cryptosporidium* is difficult to eradicate and is considered by some to be incurable[39]. More recently azidothymidine has been reported to produce a dramatic improvement in symptoms and the organism may disappear from the stool[41]. Cytomegalovirus can produce a syndrome which mimicks inflammatory bowel disease with abdominal pain, fever and bloody diarrhoea[42–45]. Diffuse or segmental ulceration of the colon occurs and histologically the disease is characterized by non-specific inflammation with dense 'owl's eye' intranuclear inclusion bodies[6]. These inclusions are most readily apparent in vascular endothelial cells in inflamed areas, which indicates that the colitis is caused by a virally induced vasculitis[46]. Major complications such as toxic dilatation, perforation and massive haemorrhage are well documented and carry a poor prognosis. Further bleeding or reperforation may occur from ulceration at other sites in the gastrointestinal tract despite adequate surgical treatment of the colonic disease[46–48]

Other less common causes of colonic symptoms in HIV positive patients include *Isospora belli*, *Mycobacterium avium intracellularis*, microsporidia, *Strongyloides stercoralis* and *Cryptococcus neoformans*[22,49]. 'AIDS enteropathy' refers to a syndrome comprising of diarrhoea, weight loss, fat malabsorption and partial villous atrophy which occurs in the absence of an identifiable pathogen[50]. The pathogenesis of this condition is incompletely understood though it has recently been suggested that it might be due to HIV itself[39].

Non-condylomatous perianal lesions in HIV positive patients

Some authors have reported severe and progressive forms of anorectal sepsis in patients with symptomatic HIV infection (CDC groups 3 and 4)[8,25]. Anal ulceration due to cytomegalovirus infection[6,26] or *Cryptococcus neoformans*[51] also appears to be confined to patients with symptomatic HIV infection. These ulcers may be distinguished from simple anal fissures by their size, induration and undermined edges. Several of these anal lesions may exist simultaneously in the same patient. Wastell has recently suggested a new term 'the gay anus syndrome' to describe the clinical picture of a homosexual male with a moist anus, often with a mucus leak, skin tags and condylomata[52]

Although postoperative healing takes place normally in male homosexuals who are HIV negative or asymptomatic HIV antibody positive (CDC group 2), it seems that patients with symptomatic HIV infection (CDC groups 3 and 4) heal poorly[8,26]. Wexner *et al.*[8] found that 88 per cent of perianal wounds had not healed within 30 days of surgery in their series of patients with symptomatic HIV infection Our experience accords with that of Wexner *et al*; some patients experience considerable morbidity for weeks or months following surgery[26]. These observations are important because, unless the subgroup of homosexual men with symptomatic HIV infection can be identified before operation by careful history taking, clinical examination, the assessment of risk factors and serological testing, they may be subjected to operative procedures which exacerbate rather than improve their perianal symptoms. If in doubt about HIV status, minimal surgical intervention is indicated[8,26].

Condylomata acuminata in HIV antibody positive patients

Condylomata are frequently present in large numbers and recurrence after excision is more likely in symptomatic HIV antibody positive than in HIV antibody negative individuals Dysplasia (anal intraepithelial neoplasia) is more commonly seen in the condylomata of symptomatic HIV positive patients[53,54]. The natural history of these dysplasias has not been fully established, but centres dealing with large homosexual populations report a dramatic increase in the incidence of both carcinoma *in situ* and invasive anal squamous cell carcinoma[54,55]. In patients with symptomatic HIV infection conservative treatment of condylomata is advised because, as in other forms of perianal disease, postoperative healing is poor[8,46]. Suspicion of dysplastic or malignant change justifies biopsy and histological examination[54,56].

Malignancy in HIV positive patients

The association between immunosuppression due to symptomatic HIV infection and the development of malignancy has recently been recognized[6,8,22,25,26,39,46,48,56–58]. The three most common malignancies are anal squamous cell carcinoma, Kaposi's sarcoma and non-Hodgkin's lymphoma.

Anal squamous cell carcinoma is a rare tumour However, there appears to be an increasing incidence of this tumour in association with HIV infection[8,57]. Though local excision may have a role in the treatment of small anal verge carcinomas, there is increasing evidence that the optimal treatment options for anal verge and anal canal lesions are either radiotherapy or a combination of chemotherapy and irradiation[58,59]. Surgery should now be reserved as a salvage procedure if there is a poor response to or local recurrence after non-surgical treatment. In patients with symptomatic HIV infection the prognosis is poor.

Kaposi's sarcoma is an aggressive tumour in patients with HIV infection. Fulminating gastrointestinal manifestations such as torrential haemorrhage, perforation or intestinal obstruction may precede the more usual cutaneous manifestations of this disease[46,48,56]. Kaposi deposits are typically haemorrhagic, plum coloured raised lesions which can occur in any part of the gastrointestinal tract and often coalesce to form large plaques. Although these lesions produce a characteristic umbilicated appearance on barium enema examination[60], endoscopy is the mainstay of diagnosis[61] From the practical point of view, biopsy is dangerous because of the risk of profuse haemorrhage and may be unhelpful as the deposits are submucosal[62].

Non-Hodgkin's B cell-derived extranodal lymphomas have also been described in patients with symptomatic HIV infection. These may occur at any site in the gastrointestinal tract; the patients may present with weight loss and an abdominal mass. Acute presentations include obstruction, perforation and haemorrhage[9,46,48,63,64].

Primary anorectal lymphoma has recently been described as a cause of local anal symptoms such as bleeding, pain, discharge, ulceration and sepsis. HIV-associated anorectal lymphoma has been noted to occur in younger patients and to run a more aggressive course than in non-HIV infected patients[8,46,65–68]

Both Kaposi's sarcoma and gastrointestinal lymphoma are primarily treated by chemotherapy[46,56]. These tumours follow an aggressive course and carry a poor prognosis Surgery has a limited place in the elective management of these conditions, but is indicated for life-threatening complications such as perforation or haemorrhage. Nevertheless, operative intervention may carry high postoperative morbidity and mortality rates[8,48,69–71].

Discussion

The present review illustrates that male homosexuals are at risk of developing a wide variety of colorectal and perianal diseases A high index of suspicion coupled with a careful sexual history in those patients thought to be at risk provides the cornerstone of diagnosis and should lead to increased recognition of these diseases.

In HIV negative individuals, the treatment of colorectal and perianal lesions seldom presents major problems. By contrast, the diagnosis and management of these diseases in patients with symptomatic HIV infection (CDC groups 3 and 4) can be difficult. HIV infection increases the spectrum of lesions and there is increasing evidence to indicate that surgical treatment is associated with poor healing and high postoperative morbidity and mortality rates. In order to avoid these problems, the clinician should attempt to distinguish patients who are HIV negative or HIV positive asymptomatic (CDC group 2) from those who have symptomatic HIV infection.

Currently, HIV testing can only be performed with fully informed consent. Furthermore, the recognition of symptomatic HIV infection may be difficult because some patients may have no manifestations of immunodeficiency at the time of presentation with colorectal or perianal disease. Hence, surgeons have to rely on their own assessment of risk factors such as recurrent venereal infections, promiscuity, HIV status of previous partners and recurrent opportunistic infections in order to determine the likelihood of symptomatic HIV infection.

The management policies for HIV patients are similar to those for patients with hepatitis B infection. These policies are outside the scope of the present review but are adequately covered elsewhere[72,73]. The HIV is much less infective than the hepatitis B virus and the risk of seroconversion following a needlestick injury is probably less than 1 per cent[74].

Although it has been suggested that all homosexuals should be considered as being at high risk of HIV infection[21], this attitude ignores the presence of low risk individuals within the homosexual population. If, after careful evaluation, doubt still exists about likely HIV status, these patients should be treated as at risk for symptomatic HIV infection and conservative therapy is advised.

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For debate

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Patient throughput and mortality rate in a trauma service

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Trauma centre standards of the American College of Surgeons set a minimum annual volume of cases for trauma surgeons. The volume requirement, however, lacks an objective basis. The author reviews a personal series of cases revealing considerably lower volume than recommended, while injury severity and mortality were comparable to published data. No death was considered preventable on review. Possibly, lower individual caseloads are acceptable for trauma surgeons.

Keywords: Trauma, mortality rate

In recent years, trauma centres have been designated according to the amended standards proposed by the American College of Surgeons (ACS) Committee on Trauma[1]. This paper examines the standard detailing the requisite annual caseload for individual trauma surgeons. The ACS guidelines call for 'fifty severe and urgent cases per year' (per surgeon); since all such standards when utilized in the designation process have therapeutic and economic consequences, it is imperative that they have an objective basis.

Patients and methods

Consecutive trauma admissions for a 3-year period were identified. Eighty-five patients were treated, providing an average of 28 annually. All admissions were to the Wilkes-Barre General Hospital, which functions as a level II institution in a voluntary regional trauma system. No surgical residents are involved in patient care, a defined field triage method and in-house resuscitation team (headed by the trauma surgeon) are in place. A quality assurance programme, mortality review and multidisciplinary trauma conference have been developed. Trauma surgery is performed by those members of the general surgery section who voluntarily participate in the trauma programme, pledging early availability during a (rotating) 24-h period No elective surgery is scheduled by that surgeon during this period. Surgeons not on call function in a back-up capacity, in the event the primary surgeon is unavailable, it is his responsibility to designate (in advance) a covering surgeon from among those on the trauma service Resuscitation is aided by emergency medicine specialists who are continuously available in the trauma receiving area Nurses at every phase of trauma care have received formal trauma training In-hospital nurse anaesthetists and operating room staff, as well as readily available anaesthetists, participate in resuscitation and surgical care Seriously injured patients are all admitted to the same surgical intensive care unit. There, care is administered according to the preference of the individual surgeon the author, for example, provides comprehensive critical care while some other trauma surgeons share care with pulmonary medicine, cardiology and nephrology specialists.

In order to assess the severity of injury, the incidence of intensive care unit admission, ventilator requirement, necessity for surgery, and presence of shock on admission were noted (The latter was defined by a systolic blood pressure of less than 90 mmHg.) Age, injury severity score, lowest trauma score within 1 h of admission, and mortality were also recorded

Injury severity and mortality were compared with available reports from other trauma facilities (Reference 2 and W. S. Copes, personal communication). Each death was subjected to Triss (trauma score, injury severity score, age) analysis[3] to determine the statistical probability of survival. Triss analysis is based on anatomical factors via injury severity score, physiological data by means of trauma score, and age, each of which has been shown to correlate with survival[4–6]. A death in a patient with a probability of survival greater than 50 per cent is considered statistically unexpected A blind review of the deaths by a trauma director in a level I institution was also utilized to determine whether any were preventable.

Results

Eighty-five patients were admitted to the author's trauma service over a 3-year period, providing an average of 28 per year. Six deaths occurred, yielding a 7 per cent mortality rate. Causes of death are listed in Table 1. The mean severity criteria among those dying compared with the survivors are noted in *Table 2*, while severity criteria for the entire series are found in *Table 3*.

One death followed a blunt trauma cardiac arrest with indications for immediate thoracotomy, followed by laparotomy (patient 1). A second death (patient 2) occurred in an initial survivor of a prehospital cardiac arrest (pedestrian struck by vehicle), who required urgent thoracotomy. Patient 3, following an automobile accident, had a closed head injury resulting in subarachnoid haemorrhage. His pupils were fixed and dilated on admission. Patient 4, suffering a fall, also died of inoperable brain injuries (diffuse intracerebral haemorrhage) A strangulation victim (patient 5) suffered central nervous system hypoxia and brain death. A severe bellows-type decompression asphyxiated patient 6, who had a four-storey fall, presenting with bilateral pulmonary parenchymal haemorrhage leading to massive haemoptysis which occurred during laparotomy for abdominal injuries.

Triss analysis[3] provides a predicted survival percentage for each death. Five of six had a probability of survival of <50 per cent and therefore might be statistically predicted to die. Only patient 6 (who also had midface fractures, multiple extremity fractures, ruptured spleen, retroperitoneal haematoma, skull fracture and profound shock at admission) had a probability of survival of >50 per cent. Autopsy confirmed the nature of this pulmonary haemorrhage.

Outside blinded review clinically assessed all deaths from the medical record. No death was judged preventable in this series.

Table 1 *Deaths occurring in the study period*

Patient	Age (years)	Cause of death	Trauma score	Injury severity score	Probability of survival
1	18	Haemorrhage	1	66	0
2	71	Sepsis	10	35	0.47
3	17	Head injury	7	33	0.17
4	76	Head injury	9	26	0.26
5	25	Hypoxia	1	41	0
6	21	Hypoxia	12	34	0.94

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Table 2 *Comparison of mortality in the present study with the Yale study and the Major Trauma Outcome Study*

	Present study	Yale*
Total cases	84	191
Total deaths	6	20
Percentage mortality rate	7	10·5
ISS (overall mean)	18·6	22·5
ISS (survivors mean)	17	18
ISS (non-survivors mean)	39	41

	Present study	Major trauma outcome study†
Percentage mortality	7	10
Mean ISS survivors blunt trauma (age 15–54 years)	16	12·2
Mean ISS non-survivors blunt trauma (age 15–54 years)	44	30·8
Mean ISS survivors blunt trauma (age ≥55 years)	18	11·2
Mean ISS non-survivors blunt trauma (age ≥55 years)	30	25·9
Mean ISS survivors penetrating trauma‡ (age 15–54 years)	24	11
Mean ISS survivors penetrating trauma‡ (age ≥55 years)	20	10·5

ISS, injury severity score; *Reference 2; †W S Copes, personal communication; ‡no deaths among penetrating trauma patients in this series

Discussion

The hospital resources document of the Committee on Trauma of the American College of Surgeons[1], referring to trauma surgeons, states, 'attending ... might be considered to have adequate experience in trauma surgery if they treat approximately fifty severe and urgent cases per year.' Unfortunately, there is a dearth of objective data examining the influence of quantity on the quality of care by an individual. The ACS document supports the 50 cases per year position solely by citing Luft *et al.*[7]. Interestingly, this paper does not study trauma, but analyses the effect of hospital-wide surgical volume on mortality for specific elective procedures. Fifty abdominal aortic aneurysm resections per year per institution, for example, were said to represent sufficient quantity to obtain a satisfactory hospital mortality rate This is the only 'objective' basis cited for the suggested minimum volume for the trauma surgeon. The lack of an objective basis for the stated standard prompted the author's review of his own volume and outcome.

Intuitively, trauma surgeons recognize the need for repetition and practice to maintain both individual and institutional skill levels. As shown, the ACS suggested minimum caseload for the individual surgeon is not based on objective data. Furthermore, the recommended trauma volume for each institution is derived as a multiple of the requirement for individual surgeons. Since trauma centre designations have widespread medical and economic consequences, it is desirable that the requirements be objective

Table 3 *Indices of severity in patients entered into the study*

	Number	Percentage
Intensive care unit admission	62	73
Ventilator requirement	24	29
Surgery	35	43
Shock on admission	16	19

The present study demonstrates an acceptable mortality rate in a personal series comprising 28 cases annually. Acceptable mortality rate is defined by the similarity to results of other institutions with expertise in trauma, statistical examination by Triss, and the findings of the outside reviewer.

Though this small series cannot be expected to establish a satisfactory threshold of ongoing experience for trauma surgeons, it suggests that 50 major cases per surgeon annually may not be necessary to preserve quality of trauma care as measured by mortality rate. Recommendations for institutional trauma volume may require downward adjustment if this study is substantiated.

In general, the standards for trauma centres set by the ACS provide rational guidelines for trauma centre preparation and designation. Nevertheless, it is probable that in an environment of institutional commitment, active general surgeons with interest in trauma care and education may function adequately with fewer than 50 cases each year. Possibly, adequate trauma experience in training may allow a lower continuing experience without detriment. Perhaps other factors, including the presence of senior surgeons, upon patient presentation may be as important as volume considerations in maintaining acceptable trauma centre mortality rates

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Prognostic index for the development of liver metastases in patients with colorectal cancer

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The incidence of synchronous and metachronous liver metastases in patients with colorectal cancer is extremely high. Approximately 25 per cent of patients will have overt liver metastases at the time of presentation, and in the remainder up to 40 per cent will eventually develop liver metastases. In an attempt to obtain a prognostic index for the prediction of those patients most likely to develop liver metastases, 134 patients with primary colorectal cancer but without overt liver metastases at initial presentation were followed up for between 5–10 years. Regular liver scans were performed and the presence of liver metastases observed. A total of 47 patients developed liver metastases. Those preoperative variables related to the subsequent development of liver metastases were sex, log_{10} serum alkaline phosphatase level and Dukes' classification. A prognostic index using these parameters has been calculated.

Keywords: Colorectal cancer, liver metastases

Patients with colorectal cancer have a high risk of developing liver metastases. It is accepted that micrometastases from the primary tumour enter the liver via the mesenteric portal venous circulation and have the potential for developing into overt metastases[1,2,3]. Previous studies have indicated that such occult liver metastases are present in up to 30 per cent of patients at the time of initial surgery. The recognition of patients with these occult metastases has required complex imaging investigations such as sequential computed tomography scanning[4], ^{99m}Tc macroaggregated albumen injections into the portal vein[5], intraoperative ultrasound[6] and the calculation of the hepatic perfusion index[7]. The present study has been designed to determine whether simple 'routine' investigations could be used to predict accurately which individual patient with colorectal cancer has a high chance of developing overt liver metastases as the predominant site of recurrent disease

Patients and methods

We have previously reported a randomized controlled trial of adjuvant portal vein cytotoxic perfusion in patients with primary colorectal cancer but without liver metastases at the time of initial surgery[8]. To compute a prognostic index of liver metastases development 134 patients, who were randomly allocated into the control (i.e. surgery only) arm of this trial, and who have been followed up for between 5 and 10 years, have been studied.

The length of history and whether weight loss had occurred were recorded. Before operation each patient had a full blood count and liver function tests performed. In addition either an ultrasound scan of the liver or a ^{99m}Tc-sulphur colloid liver scan was performed to ensure, as far as possible, that overt liver metastases were not present at the time of initial surgery Other variables recorded included the surgeon's impression of the degree of fixity of the tumour (i.e. mobile, moderately adherent, tethered, or densely adherent with the possibility of the tumour remaining locally), Dukes' classification and the degree of differentiation of the tumour.

All patients were followed up quarterly for the first year and then at half-yearly intervals. Liver function tests and liver scans (usually ultrasound) were performed at each visit in the majority of cases.

A total of 47 patients developed liver metastases. If death occurred in a patient with known recurrence, and a post mortem was not performed, then the metastases were assumed to be the cause of death

Results

A stepwise multivariate regression analysis using the BMDP® statistical package (BMDP Statistical Software, Los Angeles,

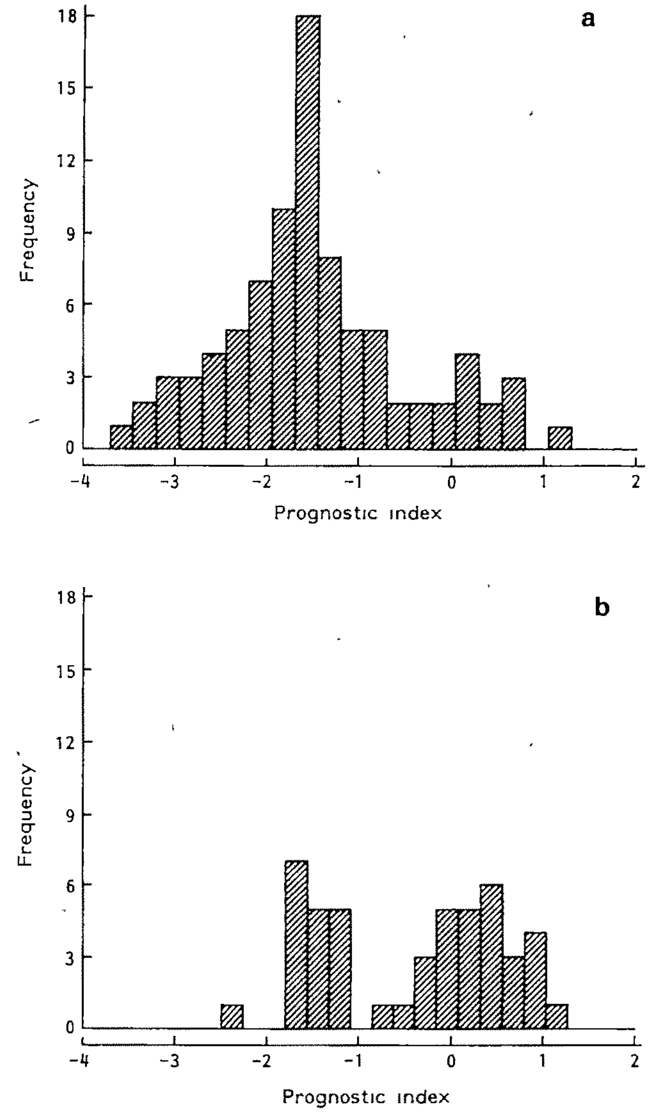

Figure 1 *Frequency histograms for* **a** *the prognostic index of patients without liver metastases, and* **b** *the prognostic index of patients with liver metastases*

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Table 1 *Survival analysis based upon the Cox proportional hazards regression model of patients with* (n=47) *and without* (n=87) *liver metastases*

Variable		Coefficient	Odds ratio (no change in risk=1)	χ^2	*P*
Full model					
Age at operation	Years	−0·0040	0·9587	0·039	0·84
Sex	1=Male 2=Female	0·9502	2·5862	4·091	0·04
Length of history	Months	−0·0194	0·9349	0·130	0·72
Log$_{10}$ haemoglobin	g/l	−1·8653	0·8822	0·303	0·58
Log$_{10}$ white cell count	10^9/l	−0·3594	0·9941	0·194	0·66
Log$_{10}$ platelets	10^9/l	−0·9183	0·8568	0·260	0·61
Log$_{10}$ serum bilirubin	μmol/l	0·5273	1·1105	0·210	0·65
Log$_{10}$ serum alkaline phosphatase	units/l	−1·9530	0·6638	3·946	0·05
Log$_{10}$ serum SGOT (AST)*	units/l	0·3313	1·0753	0·136	0·71
Weight loss	1=Yes 2=No	0·0151	1·0152	0·001	0·97
Wound infection	1=Yes 2=No	0·4227	1·5261	0·320	0·57
Chest infection	1=Yes 2=No	0·3725	1·4514	0·664	0·42
Anastomotic breakdown	1=No 2=fistula (1 week) 3=fistula (1–3 weeks) 4=fistula (4 weeks)	0·0016	1·0016	0·000	1·00
Length of postoperative hospital stay	Days	−0·0051	0·9618	0·023	0·88
Dukes' B	0=Absent 1=Present	1·7317	5·6503	31·93	<0·01
Dukes' C	0=Absent 1=Present	3·6521	38·5555		
Moderately well differentiated	0=Absent 1=Present	0·2532	1·2881	1·03	0·29
Poorly differentiated	0=Absent 1=Present	−0·5708	0·5651		
Moderately fixed	0=Absent 1=Present	−0·5505	0·5767	3·44	0·06
Densely adherent/tumour remaining locally	0=Absent 1=Present	0·4376	1·5490		
Condensed model					
Sex	1=Male 2=Female	0·5047	1·6565	2·829	0·09
Log$_{10}$ serum alkaline phosphatase	units/l	−1·6517	0·6901	7·072	0·01
Dukes' B	0=Absent 1=Present	1·5356	4·6441	43·417	<0·01
Dukes' C	0=Absent 1=Present	3·3474	28·4287		

* Serum glutamic oxaloacetic transaminase

USA)[9] and based upon the Cox proportional hazards regression model[10] was performed on 17 covariates. The end-point used was the detection of liver metastases. Patients with no evidence of liver metastases were treated as censored observations. Odds ratios and χ^2 values for the change in deviances due to the removal of each covariate are given in *Table 1*. The variables that were related to development of liver metastases at a significance level of less than or equal to 0·05 were then chosen as the predictors of liver metastases and re-entered into the analysis to compute the condensed model.

From this condensed model a function was constructed to calculate a prognostic index as follows: Index = 0·50 (if female) − 1·65 × log$_{10}$ alkaline phosphatase + 1·54 (if Dukes' B) + 3·35 (if Dukes' C).

Histograms of the index were constructed separately for patients with and without liver metastases (*Figures 1a* and *1b*). A number of cut-off values of the index were chosen above which the index is deemed prognostic, and for each cut-off value the sensitivity and specificity were calculated. For example, at a cut-off level of −1·5, sensitivity of 0·79 and specificity 0·59 were achieved, and at a cut-off level of −1·25, sensitivity was 0·68 and specificity was 0·67. A receiver operating characteristic (ROC) curve[11,12] was constructed to examine the prognostic index's ability to distinguish between those patients who developed and those who did not develop liver metastases, for a range of cut-off levels (*Figure 2*).

Beck and Schultz[11] stated that any reasonable diagnostic test will display a ROC curve in the upper left triangular region. Metz[12] further stated that, if the decision maker uses available information in a proper way, the slope of the ROC curve must steadily decrease (i.e. it must become less steep) as one moves up and to the right of the curve. The ROC curve in *Figure 2* satisfies these two criteria.

Finally, survival curves, using the BMDP statistical package to produce survival distributions based on the product-limit method[13], were plotted using different cut-off values of the prognostic index to discriminate between those greater than or equal to the cut-off value and those less than the cut-off value. An index value of −1·4 was chosen to maximize the sensitivity while retaining a high specificity. The survival curves for groups

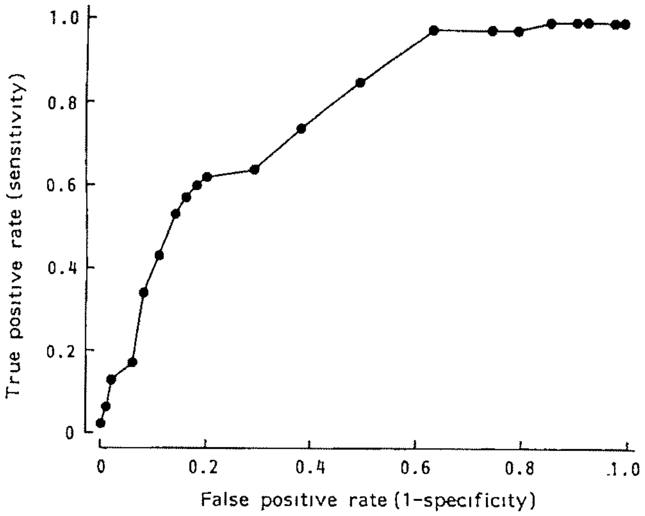

Figure 2 *Relative operating characteristic (ROC) curve for the prognostic index of liver metastases*

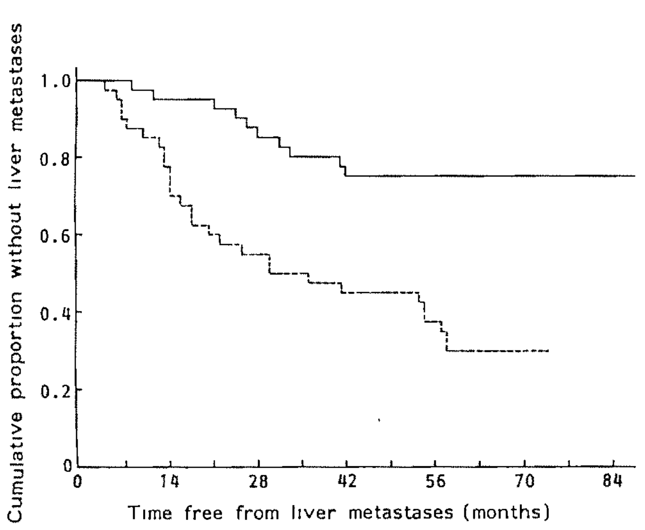

Figure 3 *Survival curves comparing patients with a prognostic index less than a cut-off value of −1·4 (——) versus those with a prognostic index greater than or equal to −1·4 (- - -).* $\chi^2 = 18\cdot79$*, d.f. = 1,* $P < 0\cdot001$ *(log rank test)*

above and below this cut-off value are given in *Figure 3*. The corresponding sensitivity and specificity were 0·74 and 0·62, respectively and the positive predictive value was 51 per cent (*Table 2*). A χ^2 value of 18·79, d.f. = 1, $P < 0\cdot001$, (log rank test) was calculated for the difference between the survival curves

Discussion

Up to 30 per cent of patients with primary colorectal cancer will have occult liver metastases at the time of initial surgery and this will clearly influence prognosis. The recognition of such patients may be of importance if adjuvant treatment directed towards the liver is advocated. Recent studies have suggested that the measurement of the hepatic perfusion index using dynamic scintigraphy[7] may recognize such patients but such technology is complicated and not generally available.

In this study we have attempted to compute a prognostic index for the development of overt liver metastases using preoperative investigations which are routinely performed in patients with colorectal cancer. The most significant variables related to the development of liver metastases were sex, $\log_{10}$ serum alkaline phosphatase and Dukes' classification.

Table 2 *Example of the ability of the prognostic index to predict liver metastasis development when applied to the data set used to construct the index. Sensitivity = 0·74, specificity = 0·62*

	Prognostic index		
	≥ −1·4	< −1·4	Total
Liver metastases			
Present	35	12	47
Absent	33	54	87

Sensitivity = 35/47 = 0·74, specificity = 54/87 = 0·62, and positive predictive value = 35/68 = 0·51

The existence of such predictive indices which include a change in serum alkaline phosphatase level adds further weight to the concept of the existence of occult liver metastases

Using a cut-off level of −1·4 for the index value, a sensitivity and specificity of 0·74 and 0·62 respectively, were achieved. Clearly the index is unlikely to perform as well on a different data set since we have used the same data for developing the index as for prediction. The index requires confirmation in a prospective study and this is in hand. However, the index is simple to calculate and may well act as a useful adjunct to patient management, particularly if selection of patients for adjuvant cytotoxic liver perfusion is contemplated.

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Metachronous colorectal carcinoma

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During the period 1943–67, 903 Danish patients aged <40 years had colorectal carcinoma. The patients were followed up for up to 41 years and during this period 44 of 501 (9 per cent) operated on for cure developed a metachronous colorectal carcinoma. The cumulative risk of a metachronous colorectal carcinoma was 30 per cent after up to 41 years of observation. The occurrence of a metachronous colorectal carcinoma was evenly distributed in the observation period. The cumulative survival rate after operation for a metachronous colorectal carcinoma was 41 per cent after 20 years of observation. We propose a lifelong follow-up programme after resection of colorectal carcinoma for cure in this age group, including annual Hemoccult® test and colonoscopy at 3-year intervals.

Keywords: Metachronous, colorectal, carcinoma

A second, metachronous colorectal carcinoma has been reported to occur in 1–7 per cent of patients with colorectal carcinoma[1–15]. However, these figures are not directly comparable and some of them may be questioned because of different definitions of metachronous carcinoma, small patient series and a short observation period. Furthermore, the observation time is not taken into account, when the risk of developing a metachronous carcinoma is given by an overall incidence rate.

The purpose of the present study is to estimate the incidence of metachronous colorectal carcinoma in young patients with colorectal carcinoma and, on this basis, to propose a programme of follow-up after primary resection for cure in this patient group

Patients and methods

A total of 43 217 Danish patients with colorectal carcinoma were reported to The Danish Cancer Registry during the period 1943–67 Among these, 1100 (2·5 per cent) were <40 years of age at the time of the diagnosis, i e. an annual incidence rate of 10·5 per 1 million inhabitants. Examination of the medical records resulted in exclusion of 114 patients with an incorrect diagnosis. Among the remaining 986 patients colorectal cancer was first diagnosed at autopsy in 35 cases Subsequently 951 patients formed the basis of a study of survival data at the end of 1977, the results of which were published previously[11].

The present study concerns a new analysis of survival and of the incidence of metachronous colorectal carcinoma at the end of 1987 Forty-seven of the 951 patients were excluded because of familial adenomatous polyposis and one because of colonic rhabdomyosarcoma. The status at the end of 1987 (alive, dead, emigrated, fate unknown) of those patients alive at the end of 1977 (when the first study was completed[11]) was sought in the Central Danish Person Register (containing demographic data of all Danish citizens), The Danish Cancer Registry (containing information on all cases of malignant disease), The Central Hospital Discharge Register (containing information about hospital discharges), hospital records and in The National Board of Health (copies of death certificates)

All cases of recurrent or metachronous colorectal carcinoma were registered. The latter was defined as a new colorectal carcinoma diagnosed more than 2 years after the first tumour; a new carcinoma diagnosed within this time was considered as an overlooked synchronous carcinoma The differential diagnosis between recurrent colorectal carcinoma and metachronous colorectal cancer was aided by assessment of the histological tumour type in patients who developed a new tumour near the site of the previous anastomosis. In three patients the exact location of the metachronous carcinoma could not be defined because of incomplete information in the medical records.

The survival after primary and metachronous colorectal carcinoma, as well as the incidence rate of metachronous colorectal carcinoma, have been calculated according to the actuarial method, giving the probability of a metachronous tumour within a given period[16] In order to demonstrate a possible variation in the risk of developing a metachronous tumour over a short period, Nelson's modification of the actuarial method was used[17]. This gives the integrated rate of metachronous carcinoma as a function of time All differences in survival data were assessed by the log rank test, a significance level of 5 per cent was adopted.

Results

Among 903 patients, 501 (55 per cent) could be operated on for cure; in this group five had a second colorectal carcinoma diagnosed <2 years after the primary carcinoma, while 44 (9 per cent) developed a second colorectal carcinoma 3–41 years after the first tumour. The annual risk of developing a metachronous carcinoma was constant throughout the observation period (*Figure 1*). The cumulative incidence rate of a metachronous carcinoma was 30 per cent (95 per cent confidence limits 14–46 per cent) after an observation period of up to 43 years (*Table 1*). Seven patients had two metachronous colorectal carcinomas and four had one metachronous colorectal carcinoma and a uterine cancer.

Of the 44 patients developing a metachronous carcinoma 27 (61 per cent) could be operated on for cure. Their cumulative 5-year survival rate was 53 per cent (95 per cent confidence limits 13–93 per cent), compared with the cumulative 5-year survival rate of 31 per cent (95 per cent confidence limits 0–63 per cent) after resection of the primary carcinoma. When comparing the total survival curves by the log rank test, the difference in survival is not significant ($0{\cdot}05 < P < 0{\cdot}1$; *Figure 2*).

Discussion

In the literature, metachronous colorectal carcinoma has been reported to occur with an overall incidence rate of 1–7 per cent[1–15] However, the results of these series are difficult to evaluate and compare for several reasons First, the definition varies to allow diagnosis of a second carcinoma at a range of 6 months to 3 years after the diagnosis of the primary tumour. Second, the overall incidence rate is a much less valuable estimate of the occurrence of metachronous carcinoma than the cumulative incidence rate, which also includes a calculation of the observation time. Finally, most of the previous studies are based on a limited number of patients and imply a relatively short observation period.

Our present study is based on all Danish patients aged <40 years of age who developed their primary carcinoma during a

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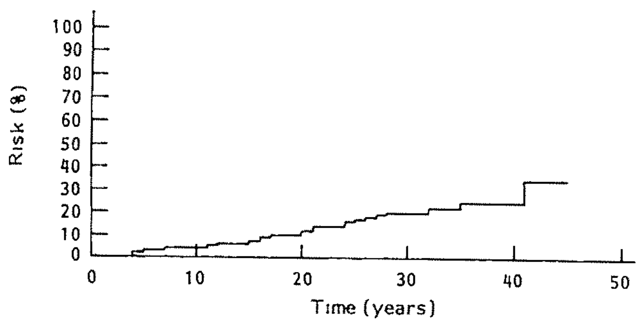

Figure 1 *Integrated risk of developing metachronous colorectal cancer (Nelson plot)*

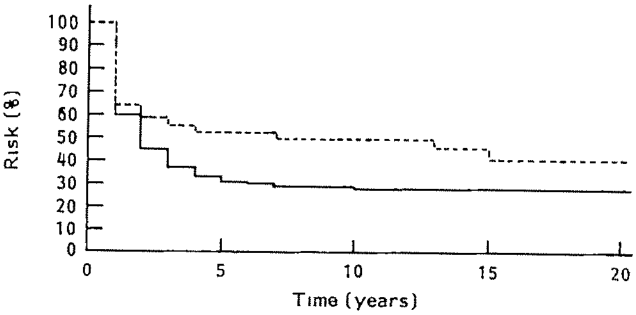

Figure 2 *Cumulative survival rate after developing primary* (n = 903) *or metachronous colorectal carcinoma* (n = 44). ——, *Primary cancer*; – – –, *metachronous cancer*

Table 1 *Observed rate of metachronous cancer calculated by the actuarial method*

Years after diagnosis	No alive at beginning of interval	No. with metachronous cancer during interval	Cumulative disease-free rate (R)	Cumulative rate of metachronous colorectal carcinoma ($1-R$)	Standard deviation
0–1	903	0	1·00	0·00	0·00
1–2	535	0	1·00	0·00	0·00
2–3	399	1	0·99	0·01	0·00
3–4	327	4	0·99	0·01	0·01
4–5	288	4	0·97	0·03	0·02
5–6	267	1	0·97	0·03	0·02
6–7	255	1	0·96	0·04	0·02
7–8	248	1	0·96	0·04	0·02
8–9	242	0	0·96	0·04	0·02
9–10	237	0	0·96	0·04	0·02
10–11	235	1	0·96	0·04	0·02
11–12	231	3	0·94	0·06	0·02
12–13	225	1	0·94	0·06	0·02
13–14	224	1	0·94	0·06	0·02
14–15	220	0	0·94	0·06	0·02
15–16	219	4	0·92	0·08	0·03
16–17	215	2	0·91	0·09	0·03
17–18	209	2	0·90	0·10	0·03
18–19	204	0	0·90	0·10	0·03
19–20	203	3	0·89	0·11	0·03
20–21	192	4	0·87	0·13	0·03
21–22	175	0	0·87	0·13	0·04
22–23	166	1	0·86	0·14	0·04
23–24	151	2	0·85	0·15	0·04
24–25	138	1	0·85	0·15	0·04
25–26	125	2	0·83	0·17	0·04
26–27	111	1	0·83	0·17	0·04
27–28	103	1	0·82	0·18	0·04
28–29	91	0	0·82	0·18	0·04
29–30	82	0	0·82	0·18	0·04
30–31	71	0	0·82	0·18	0·04
31–32	57	1	0·80	0·20	0·04
32–33	42	0	0·80	0·20	0·04
33–34	40	0	0·80	0·20	0·04
34–35	35	1	0·78	0·22	0·05
35–36	28	0	0·78	0·22	0·05
36–37	25	0	0·78	0·22	0·05
37–38	19	0	0·78	0·22	0·05
38–39	16	0	0·78	0·22	0·05
39–40	13	0	0·78	0·22	0·05
40–41	10	1	0·70	0·30	0·08

25-year period. Because of the young age of the patients and a very long follow-up these data form a solid basis for an estimation of the true risk of developing metachronous colorectal carcinoma, i.e. a secondary carcinoma diagnosed more than 2 years after the primary carcinoma.

We found a cumulative incidence rate of 30 per cent after up to 41 years of observation. For comparison, the cumulative incidence rate of colorectal carcinoma in the Danish population is approximately 4 per cent[18]. The present cumulative incidence rate is in accordance with the results of a study from St. Mark's Hospital, London, UK[12].

Our results demonstrate a constant incidence of metachronous carcinoma with time (*Figure 1*), which is also in accordance with the St. Mark's series[12]. In smaller series in the literature most metachronous colorectal cancers were diagnosed within the first 8–11 years[1,2,4–10,12,15]. This can probably be explained by a shorter observation period, partly due to a higher patient age at diagnosis of the primary tumour, and in some studies also by the use of a wider definition, i.e. a secondary tumour diagnosed within <2 years after the first tumour. The latter definition results in inclusion of a number of overlooked synchronous carcinomas[19].

The development of metachronous carcinoma in almost one-third of patients surviving 40 years after the first tumour is a surprisingly high incidence, which supports the view of Bussey *et al.* who claim that 'the longer patients survive the first operation for intestinal carcinoma the more likely they are to develop a second growth'[13].

Do our results based on young patients then represent the risk of developing metachronous carcinoma in all patients with colorectal cancer, regardless of age? Several authors have noted that the age at diagnosis of the first tumour was considerably lower in those later developing a metachronous carcinoma[4,6,8,9,14,15], while others could not confirm this observation[1,5]. However, our series of young patients may be biased toward a higher number of metachronous tumours according to the theory of Mecklin *et al.*[20] and Mecklin[21]. In a series of 468 patients with colorectal cancer they found, among those aged less than 50 years, that 29 per cent had cancer family syndrome. On this basis they suggested that the cancer family syndrome, which implies a high tendency to develop metachronous colorectal carcinoma, is a more frequent syndrome than previously believed and, especially, more often represented among young patients. Our study did not allow an evaluation of a possible family history of colorectal carcinoma and therefore the incidence of the cancer family syndrome in our series is unknown. However, 11 of our 44 patients developing a metachronous colorectal carcinoma (25 per cent) had a history of more than two primary colorectal or uterine carcinomas and among the patients there was also a trend toward more right-sided primary cancers. As these factors are some of the major features in the cancer family syndrome, the proportion of patients in our series having this syndrome may be similar to that in the series of Mecklin *et al.*[20] and Mecklin[21]. Despite this, we believe that the main explanation of the high incidence of metachronous carcinomas in our series is probably the long survival time in these young patients, although patients with the cancer family syndrome may possibly contribute to the incidence.

In our study 27 of 44 patients (61 per cent) with metachronous colorectal carcinoma could be operated on for cure The cumulative 5-year survival rate was 53 per cent, which is similar to the results in other series[5,15] and is not significantly different from the results after surgery for cure for a primary colorectal carcinoma[22].

During the past decades the possible effects of a regular follow-up programme after operation for cure for colorectal carcinoma has been a matter of debate. A follow-up programme seems justified only if it results in prolonged survival through early diagnosis and treatment of the second (recurrent or metachronous) carcinoma. The prognosis after recurrent carcinoma is poor, as recent information suggests that even an aggressive follow-up to detect early recurrence has little or no effect; local recurrences can be resected in only 10–20 per cent of patients and the 5-year survival after such a resection is only 5–10 per cent[22].

Gilbertsen and Nelms have shown that regular proctosigmoidoscopy with removal of new adenomas can reduce the expected incidence of rectal carcinoma by 85 per cent[23] The incidence of a metachronous cancer is higher in patients with a carcinoma and synchronous adenomas than in those without adenomas[24]. Follow-up after surgery for a primary colorectal carcinoma resulted in the diagnosis of a metachronous tumour at an earlier stage than expected[12]. Furthermore, we found the prognosis after a metachronous carcinoma to be similar to that of a primary carcinoma, in contrast to the poor prognosis in patients with recurrent primary carcinoma. Moreover, patients aged <40 years have the same prognosis as older patients with colorectal carcinoma[11]; their high cumulative incidence of metachronous carcinoma, the even distribution of metachronous tumours over time and their long life expectancy therefore speak in favour of a lifelong surveillance programme.

Based on the literature on follow-up after surgery for cure in colorectal carcinoma[25] and on screening asymptomatic individuals for colorectal neoplasia[26–28] we propose a programme based on colonoscopy and examination for occult bleeding using the Hemoccult test® (SmithKline Diagnostics, Sunnyvale, California, USA). Interim results of a large ongoing screening of approximately 30000 asymptomatic individuals using the Hemoccult test (three tests repeated at an interval of 2 years) demonstrated that 1·2 per cent were Hemoccult-positive. Among these, colonoscopy detected carcinomas in 13 per cent and adenomas in 43 per cent. Compared with a control group of the same size the incidence of new carcinomas was higher and the carcinomas were diagnosed at an earlier stage, but it is not yet known whether the study will show a reduction in mortality rate[26,27]. In screening for metachronous lesions, the Hemoccult test will probably detect a similar proportion of the lesions, and colonoscopy at 3-year intervals will detect those carcinomas undetected by the Hemoccult test at an early stage. This would still allow for radical resection, as most cancers do not reach a diameter of 2 cm in <2–3 years after a 'clean colon' has been ensured[29,30]. A reduction of the interval between colonoscopies probably will have little positive effect; on the contrary, the morbidity and mortality rates from the examinations will increase[31,32].

According to the above arguments we propose the following lifelong programme. In patients aged <40 years operated on for cure an initial total colonoscopy is performed 3 months after surgery to ensure a 'clean colon', i.e. one without synchronous adenomas or carcinomas. After this an annual Hemoccult test should be carried out, leading to colonoscopy in those having occult bleeding Furthermore, colonoscopy is repeated in all patients at intervals of 3 years.

Based on the annual incidence rate of colorectal cancer in patients aged <40 years of 10 5 per 1 million inhabitants[11] and a resection rate for cure of approximately 75 per cent, the above mentioned programme will result in colonoscopy of about seven newly-diagnosed patients operated on for cure per year per 1 million inhabitants. The annual number of colonoscopies will only increase to about 30 after 10 years, provided a crude 5-year survival rate of about 40 per cent is accepted.

In conclusion, the high cumulative incidence rate of metachronous colorectal cancer in the small group of young patients indicates that a lifelong follow-up programme including regular Hemoccult testing and colonoscopy seems justified both from a cancer-prophylactic and from a cost-benefit point of view.

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Incidence of dysplasia in the anorectal mucosa in patients having restorative proctocolectomy

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The incidence of dysplasia in the mucosal strippings from the anorectal stump was studied in 132 patients treated by restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatosis. The anorectal mucosa was stripped from the level of division of the gut tube to the dentate line. Of 118 patients with ulcerative colitis, 12 (10·2 per cent) had dysplasia in some part of the large bowel. Mucosal strippings were examined histologically in 118 cases, of which only three (2·5 per cent) showed dysplasia. There was a correlation between dysplasia and the presence of carcinoma and the duration of the disease in the operative specimen of colon and rectum and also in the anorectal mucosal specimen although the number of patients with carcinoma (eight cases) in this analysis was small. All 14 patients with familial adenomatous polyposis showed large bowel mucosal dysplasia in the operative specimen which was severe in six cases. Anorectal mucosal strippings were examined in these patients and 12 showed dysplasia which was severe in three.

Keywords: Incidence, dysplasia, anorectal mucosa, restorative proctocolectomy

The purpose of restorative proctocolectomy with ileal reservoir in treating ulcerative colitis or familial adenomatous polyposis is to remove all diseased mucosa and to avoid a permanent ileostomy. The original descriptions of the procedure involved stripping of the mucosa from the anorectal stump left after removal of the surgical specimen[1]. The need for this has recently been questioned; continence after surgery is superior if the anal transitional zone mucosa is preserved while the chance of carcinoma developing in such a small area of residual mucosa is low[2]. The cancer risk in the anorectal mucosa is likely to be related to whether dysplasia is present. The present study was, therefore, undertaken to determine the incidence and severity of dysplasia in mucosal strippings taken from the anorectal stump during restorative proctocolectomy.

Patients and methods

One hundred and thirty-two patients who had anorectal mucosa available for histological examination underwent restorative proctocolectomy with ileal reservoir between January 1976 and December 1987 One hundred and eighteen had ulcerative colitis with a mean(standard deviation) age of 31·8(10·2) years and a female:male ratio of 0 89·1. Fourteen patients had familial adenomatous polyposis with a mean age of 36 5(11·3) years and a sex ratio of 0·56:1. During the same period a further 40 patients were treated including 35 with ulcerative colitis and five with familial adenomatous polyposis. Anorectal mucosa was not available from them and they have not been included. In nine cases the mucosa was not removed because the anorectal stump after division of the gut tube extended no further than 10 mm from the dentate line and in 31 cases the anorectal strippings were not sent for histology

In the initial cases the rectum was divided 6–8 cm from the anal verge[3] leaving a long stump with a large area of residual mucosa to be removed Gradually the stump was shortened and in the last 80 cases division was carried out approximately at the level of the anorectal junction. It is impossible to state precisely the extent of the mucosectomy The mucosa was removed in all cases from the most proximal part of the anorectal stump to a variable distance from the dentate line to a level usually tangential to the tips of the papillae. This therefore included the majority of the upper anal canal mucosa.

The histological sections of the resected specimen and the stripped anorectal mucosa were reviewed with particular reference to the incidence of dysplasia. Dysplasia in ulcerative colitis was graded by one of the authors according to an internationally accepted classification[4] in which specimens are categorized as negative, indefinite or positive for dysplasia The category indefinite for dysplasia is divided into three subcategories, namely probably negative, unknown and probably positive

Positive for dysplasia is divided into two subcategories, low grade dysplasia and high grade dysplasia. The incidence of dysplasia in the resected specimen and in the stripped mucosa was related to coexisting colorectal carcinoma and the duration of the disease. Although heterogeneity of the grade of dysplasia was observed in individual specimens the most advanced grade was taken to represent the grade of a given specimen

Adenomas in familial polyposis were graded into mild, moderate and severe degrees of dysplasia according to accepted histological and cytological criteria[5].

Statistics

The χ^2 test and Student's t test were used in the statistical analysis of data Percentage values were compared by calculating the standard error of the difference between the two proportions

Results

The average age of onset of ulcerative colitis was 24·5(9·8) years and the average duration of the disease from diagnosis to operation was 7·5(6 2) years A carcinoma was present in eight cases, including seven with a history of more than 10 years and one with a history of 8 years.

There were 12 cases of positive dysplasia, three of which had dysplasia in the stripped anal mucosa (*Table 1*).

In the resected specimen dysplasia was present in seven (87·5 per cent) of the eight cases with carcinoma and in five (4·5 per cent) of the 110 without. In the stripped anorectal mucosa, however, dysplasia was present in two (25 per cent) of the eight patients with carcinoma and in one (0·9 per cent) only of the 110 without (*Table 2*).

In the resected specimen dysplasia was present in two (2·5 per cent) of the 78 patients with disease duration of less than 10 years. It was present in 10 of 38 (26·3 per cent) patients with duration of more than 10 years. In the stripped mucosa

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these proportions were 0 of 78 (0 per cent) and 3 of 38 (7·9 per cent) respectively (*Table 3*).

Table 4 refers to familial adenomatous polyposis. Dysplasia was found in all specimens except for two cases of mucosal strippings. The incidence of severe dysplasia in resected specimens was 6 of 14 (42·9 per cent). In the stripped mucosa it was 3 of 14 (21·4 per cent). Carcinoma was present in one of the three cases in which adenomas with severe dysplasia were found in the stripped mucosa and in two of the eight cases with mild dysplasia (*Table 5*).

Discussion

An original purpose of restorative proctocolectomy was to remove all diseased tissue including the anorectal mucosa. Recent arguments favouring mucosal preservation include retention of important sensory receptors (and thus function, especially continence, is improved) and that the cancer risk in such a small area is exceedingly low. The anastomosis can be achieved using the mechanical stapler thereby avoiding the necessity of a perineal phase to the operation. In a recent report[2] it is suggested that continence is better when the anorectal mucosa is preserved than when a mucosectomy to the dentate line is carried out. Such difference may well be due to the anal dilatation required in the latter technique rather than to any intrinsic quality ascribable to sensation. By accomplishing an endoanal sutured anastomosis in a shorter time sphincter damage might be significantly reduced. There is evidence that damage to the internal sphincter as a result of the operation occurs[6] and it is possible to correlate leakage after surgery with reduced sphincter tone[7]. Reports of a duration of more than 30 min to construct an endoanal anastomosis have prompted the use of techniques of mucosectomy which do not stretch the sphincter[8]. There has been no comparison of function after stapled ileoanal and endoanal hand-sutured anastomosis and a randomized prospective clinical trial would be required to resolve this issue

Table 1 *Incidence of dysplasia in ulcerative colitis*

Classification of dysplasia	Resected specimen	Stripped anorectal mucosa
Negative	104	112
Indefinite	2	3
(probably negative/unknown/probably positive)	(0/0/2)	(1/0/2)
Positive	12	3
(low grade/high grade)	(4/8)	(2/1)
Total	118	118

Table 2 *Incidence of dysplasia related to the presence or absence of carcinoma in ulcerative colitis*

	No. of patients	Dysplasia (low grade/high grade)	%
Resected specimen			
With carcinoma	8	7 (1/6)	87·5
Without carcinoma	110	5 (3/2)	4·5*
Stripped anorectal mucosa			
With carcinoma	8	2 (1/1)	25⁺
Without carcinoma	110	1 (1/0)	0·9⁺

* χ^2 56·2, $P<0·001$, ⁺ χ^2 17·46, $P<0·001$

Objections to preserving the mucosa include the risk of cancer occurring in the remaining anorectal mucosa[9] and persisting inflammation causing symptoms. Persisting inflammatory symptoms have been reported in patients in whom a 1 cm cuff of columnar epithelium was preserved[10].

The results of this study have shed some light on the first of these objections. If dysplasia is regarded as indicative of malignant potential then the risk in ulcerative colitis is low. Only 2·5 per cent of all colitic patients had dysplasia but the risk may be greater when cancer is already present in the large bowel. The number of patients in this group, however, is small and further study is necessary to establish whether this is true. The length of the interval from diagnosis to surgery may also be a risk factor for dysplasia, and this would not be surprising in the light of information available in the intact colitic large bowel. In the case of familial adenomatous polyposis almost all patients in the present study had dysplasia in the anorectal mucosa and in just over 20 per cent of cases it was severe.

Our results demonstrate that a complete mucosectomy would seem to be obligatory in patients with familial adenomatous polyposis. In colitis, the case for mucosectomy is less strong although the data would suggest it to be advisable where cancer is already present in the large bowel or where the interval from diagnosis to operation is more than 10 years. The ultimate risk of cancer developing in the anorectal stump can only be determined by careful follow-up over many years.

Table 4 *Incidence of dysplasia in adenomas in familial adenomatous polyposis*

Grade of dysplasia	Resected specimen (carcinoma)	Stripped anorectal mucosa
Mild	5 (2)	8
Moderate	3	1
Severe	6 (1)	3
No adenoma	0 (1)	2
Total	14	14

Table 5 *Relationship between the grade of dysplasia in the stripped anorectal mucosa and associated colorectal carcinoma*

	Mild	Moderate	Severe	No adenoma
With carcinoma	2	0	1	1
Without carcinoma	6	1	2	1

Table 3 *Incidence of dysplasia related to the duration of ulcerative colitis*

	Duration of the disease (years)	No of patients	Dysplasia (low grade/high grade)	%
Resected specimen	<10	78	2 (1/1)	2·6*
	>10	38	10 (3/7)	26·3*
Stripped anorectal mucosa	<10	78	0	0⁺
	>10	38	3 (2/1)	7·9⁺

* χ^2 15·5, $P<0·001$, ⁺ χ^2 6·32, $P<0·05$

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Short note

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Vitamin C levels in patients with familial adenomatous polyposis

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Vitamin C influences cell growth and has been used experimentally to inhibit the growth of colorectal tumours[1,2]. Humans, who are incapable of synthesizing vitamin C, absorb it maximally in the proximal small intestine[3], an area found to be abnormal in most patients with familial adenomatous polyposis (FAP)[4]. Reports of vitamin C administration to FAP patients have shown a reduction in rectal polyp density in some postcolectomy patients[5,6]. This inconsistent effect might be explained by the slow release formulations of vitamin C used. Rapid intestinal transit may occur after colectomy (the standard treatment for FAP), reducing vitamin C to mucosal contact time, thereby decreasing both the ability of vitamin C to act locally and the time available for systemic absorption. In addition, many FAP patients alter their diet to decrease stool volume and to diminish the risk of bolus obstruction by citrus fruit pith, with a consequent low fibre and fruit intake. These features might produce a sub-clinical vitamin C deficient state in FAP patients, as well as prejudicing the mode of action of administered vitamin C.

We therefore measured leucocyte ascorbic acid levels in three outpatient groups: healthy FAP patients (postcolectomy), chronic disease patients and normal controls Leucocyte ascorbic acid levels in FAP patients were analysed according to the density and type of gastroduodenal disease[4].

Patients and methods

Of 55 postcolectomy outpatients with FAP studied, 52 had undergone gastroduodenoscopy within the previous year Duodenal adenomas were found in 50 of these patients, in five of whom the adenomas were not visible macroscopically (microadenomas). Of the two patients without adenomas, one had hyperplastic changes in the duodenum on biopsy. Duodenal disease was graded as mild, moderate or severe according to criteria of polyp density and type All FAP patients had undergone colectomy. Seventeen chronic disease outpatients (rheumatoid arthritis, eight, complicated insulin dependent diabetes mellitus, two; ulcerative colitis, two; colonic Crohn's disease, one; coeliac disease, one, chronic duodenitis, one; lymphoma, one, and chronic duodenal ulcer, one) were studied Twenty-eight control patients (20 outpatients with minor indications, eight staff members) were studied. Patients taking vitamin supplements were excluded Smoking history was obtained The technique to measure leucocyte ascorbic acid was that of Gibson *et al.* 1966[7], and the results expressed in $\mu g/10^8$ white blood cells. Statistical analysis was by the Wilcoxon rank sum test, and the index of dispersion was expressed as the interquartile range.

Results

The mean leucocyte ascorbic acid level was significantly lower in FAP (18·08 $\mu g/10^8$ white blood cells) and chronic disease patients (18·07 $\mu g/10^8$ white blood cells) than in controls (25·4 $\mu g/10^8$ white blood cells), $P<0{\cdot}01$ (*Table 1*). There were more smokers in the FAP group but no significant difference in the mean leucocyte ascorbic acid between FAP smokers (18·55 $\mu g/10^8$ white blood cells) and non-smokers (17·85 $\mu g/10^8$ white blood cells). The mean leucocyte ascorbic acid level in FAP patients with mild duodenal disease ($n=11$, leucocyte ascorbic acid $=19{\cdot}14$ $\mu g/10^8$ white blood cells) was not significantly different from the level found in those with moderate and severe duodenal disease ($n=41$, leucocyte ascorbic acid $=17{\cdot}37$ $\mu g/10^8$ white blood cells), $P>0{\cdot}1<0{\cdot}2$). The mean leucocyte ascorbic acid in patients with a normal stomach ($n=19$, leucocyte ascorbic acid $=18{\cdot}82$ $\mu g/10^8$ white blood cells) was not significantly different from the level found in patients with gastric abnormalities (polyps, gastritis – $n=33$, leucocyte ascorbic acid $=17$ 12 $\mu g/10^8$ white blood cells), $P>0{\cdot}1<0{\cdot}2$.

Discussion

Vitamin C may influence cell growth either by local or systemic actions[5] Locally, vitamin C acts as an antioxidant which could inhibit the formation of carcinogenic *N*-nitroso compounds or alkylating agents[8], interfere with faecal steroid metabolism by affecting anaerobic intestinal bacteria[5], or help defend against oxygen-radical induced DNA damage[9,10]. Otherwise, circulating carcinogenic alkylating agents absorbed in the enterohepatic circulation may be systemically inactivated[8].

A population based study of 715 colorectal cancer cases and

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Table 1 *The results of leucocyte ascorbic acid levels in the three groups*

	n	Sex (M)	Smokers	Mean age (years)	Mean LAA (μg/10^8 WBC)	Median LAA (μg/10^8 WBC)	Range of LAA (μg/10^8 WBC)	Interquartile range (μg/10^8 WBC)
FAP	55	29	18	41	18·08*	17·38	5·16–37·2	12·72–23·38
Chronic disease	17	9	4	50	18·07	15·19	8·08–32·88	10·14–20·65
Normals	28	14	4	38	25·4*	25·55	14·26–36	21·39–29·12

FAP, familial adenomatous polyposis; LAA, leucocyte ascorbic acid, WBC, white blood cells; * $P<0{\cdot}01$ Wilcoxon rank sum test

727 age and sex matched controls noted that cancer cases were significantly less likely to use vitamin C supplements than controls, although it was not possible to show that lack of vitamin C supplementation had an independent impact on cancer generation[11]. Nevertheless, a subtle effect seems likely

Our study has shown low leucocyte vitamin C levels in polyposis patients. This may be because of poor absorption caused by intestinal hurry, or because of low dietary intake, related to advice to limit fruit intake for fear of pith bolus obstruction, or because vitamin C metabolism in polyposis patients is different from others. Although the leucocyte vitamin C level bore no relationship to the severity of duodenal polyposis, FAP patients nevertheless differ from controls in that the duodenal mucosa is abnormal in FAP, as indeed may be other areas of small bowel mucosa. The low leucocyte ascorbic acid may thus reflect a defect in vitamin C absorption at the cellular level, regardless of the macroscopic extent of disease, on which severity grading is partially based[4].

Whatever the correct explanation for the low leucocyte vitamin C level found in FAP, the use of slow release preparations in studies of adjuvant vitamin C in polyposis is likely to be less effective than more biologically available preparations. We recommend that future studies of vitamin C in FAP avoid slow release formulations and monitor leucocyte vitamin C levels.

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'Close shave' in anterior resection

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Of 192 anterior resections for rectal cancer performed over 10 years by one author (R.J.H.), 169 (88 per cent) included total mesorectal excision and all included lavage of the clamped distal rectum. Of this series, 152 (79 per cent) were classed as curative, 110 with a resection margin > 1 cm and 42 with a resection margin $\leqslant 1$ cm. The group with a > 1 cm margin had a significantly lower Dukes' A to B ratio than the group with a margin $\leqslant 1$ cm, although the proportion with Dukes' C lesions was similar in both groups ($\chi^2=6{\cdot}712$; $\mathrm{P}=0{\cdot}035$). There were no local recurrences in the latter group (95 per cent confidence interval (CI) is 0–5·9 per cent) while there were four (3·6 per cent) in the former group (95 per cent CI is 0·8–7·4 per cent). There were no significant differences in recurrence rates, local and distant, between the two groups (Fisher's exact test, $\mathrm{P}=0{\cdot}2$). Reduction of resection margin, provided total mesorectal excision and washout is properly performed, does not increase local recurrence or compromise survival.

Keywords: Carcinoma of the rectum, total mesorectal excision, resection margin, anterior resection

Recent critical appraisal of the 5 cm rule[1,2] has led to the suggestion that the distal resection margin in anterior resection for rectal cancer may be reduced and the number of abdominoperineal excisions kept to a minimum.

Patients and methods

From 1978 prospective records were kept on computer of all anterior resections performed by one author (R.J.H.) at Basingstoke. All rectal cancer specimens fixed unpinned in theatre were later opened, pinned and photographed by a consultant pathologist who accurately measured the distal resection margins. The relevant stapler 'doughnut' was separately examined and represented approximately an extra 0.5 cm. Regular follow-up included rectal examination and endoscopy by a consultant oncologist and surgeon with data recording by a full-time research assistant with close personal knowledge of all patients. An independent statistician (W.R.S.N.) analysed the relationship between distal resection margin and local recurrence.

Results

The series consists of 192 anterior resections, 152 (79 per cent) of which were classed as curative and 40 (21 per cent) of which were classified as non-curative because of metastases in 23 (12 per cent) or failed local clearance in 17 (8·8 per cent). During the same period 21 abdominoperineal excisions were undertaken, representing 9·8 per cent of all rectal cancers. Analysis of the anterior resections by resection margin size showed that 55 (29 per cent) margins were $\leqslant 1$ cm and 26 of these were $\leqslant 0{\cdot}5$ cm. The $\leqslant 1$ cm and > 1 cm margins were evenly distributed throughout the 10-year period. Total mesorectal excision was performed in 88 per cent of the patients and all had water lavage of the rectum distal to the clamp. This paper considers specifically those patients whose surgery was completed with a hope of 'cure'.

Curative anterior resections

The analysis of 152 curative anterior resections is summarized in *Table 1*; of these, 42 cases (28 per cent) had a resection margin < 1 cm and 110 cases (72 per cent) had a resection margin > 1 cm.

The < 1 cm group had a higher Dukes' A to B ratio but the proportion of Dukes' C tumours was similar in the two groups ($\chi^2=6{\cdot}712$; $P=0{\cdot}035$). There was no significant difference with regard to tumour differentiation. The < 1 cm group contained significantly lower tumours, at a mean of 4·7 cm from the anal verge at sigmoidoscopy compared with 9·5 cm for the other group ($t=8{\cdot}84$; $P<0{\cdot}001$). There were no local recurrences in the 42 curative anterior resection patients with a margin < 1 cm. The 95 per cent confidence interval (CI) for this was 0–5·9 per cent. Three (7·1 per cent) patients have developed distant metastases with a mean time to presentation of 1·9 years.

Of 110 patients with curative resection with a margin > 1 cm, four (3·6 per cent) have developed local recurrence. The 95 per cent CI for this is 0·8–7·4 per cent. The mean time to presentation with local recurrence was 1 year. Analysis of these four local recurrences suggested a potentially preventable surgical cause for each (*Table 2*). In this group a further 11 (10 per cent) patients developed distant metastases with a mean time to presentation of 1·8 years.

Statistical analysis showed no significant difference in either local recurrence rates or distant metastases in the two groups (Fisher's exact test).

Non-curative anterior resections

The classification of 40 non-curative anterior resections is complex. Thirteen had a resection margin $\leqslant 1$ cm and 27 had a margin > 1 cm. There was no significant difference with regard to tumour staging or differentiation, and the $\leqslant 1$ cm group contained significantly lower tumours at a mean of 5·1 cm from the anal verge at sigmoidoscopy compared with 9·5 cm for the other group ($t=3{\cdot}99$; $P<0{\cdot}01$).

In the $\leqslant 1$ cm group seven patients had no metastases but doubtful local clearance; only one of these developed local recurrence. In four of the remainder, complete local clearance was achieved despite distant metastases; none of these developed local recurrence. The last two patients were known to have distant metastases and incomplete local clearance, both developed early local recurrence.

In the > 1 cm group ten patients had no metastases but doubtful local clearance; only one of these developed local recurrence. In 12 of the remaining 17, local clearance was achieved despite the presence of distant metastases; none of these developed local recurrence. The last five patients were known to have distant metastases and incomplete local clearance; these patients all developed local recurrence.

Comparing the $\leqslant 1$ cm with the > 1 cm group as a whole revealed no significant difference in local recurrence rates and the same conclusion was reached after analysis of the minor subgroups

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Table 1 *Clinical details of 152 curative anterior resections comparing patients with ≤1 cm margin of tumour clearance with those with >1 cm margin*

	Tumour clearance			
	≤1 cm margin	>1 cm margin	Statistical test	Probability
Number of resections	42	110	–	–
Dukes' classification A	15	19		
B	13	53	$\chi^2=6{\cdot}712$	$P=0{\cdot}035$
C	14	38		
Differentiation Well	13	27		
Moderate	21	64	$\chi^2=0{\cdot}892$	$P=0{\cdot}64$
Poor	8	19		
Tumour distance from anal verge in cm*	4·7(1·4)	9·5(2·9)	$t=8{\cdot}84$	$P<0{\cdot}001$
Anastomotic distance from anal verge in cm*	3·4(0·9)	5·8(2·0)	$t=7{\cdot}33$	$P<0{\cdot}001$
Tumour clearance in cm*	0·7(0·4)	3·3(1·6)	–	–
Number of anastomotic leaks	8	12	$\chi^2=1{\cdot}122$	$P=0{\cdot}29$
Number of local recurrences	0	4	FET	$P=0{\cdot}27$
Time to local recurrence in years*	–	1(1·24)	–	–
Number of distant recurrences	3	11	FET	$P=0{\cdot}424$
Time to distant recurrence in years*	1·9(1·2)	1·8(1·2)	–	–
Deaths	10	39	$\chi^2=1{\cdot}391$	$P=0{\cdot}238$

FET, Fisher's exact test; * values are mean(s.d.)

Table 2 *Details of four local recurrences in the group of 110 curative resections with a resection margin >1 cm*

Sex	Age at operation (years)	Dukes' classification	Tumour differentiation	Height above anal verge (cm)	Clearance (cm)	Time to recurrence (years)	Type of recurrence	Course	Cause of local recurrence	Comment
Male	77	A	Moderate	7	2·5	2·75	Pararectal nodule Biopsy suggestive of tumour	Radioactive gold Recurrence cleared completely Well 8 years after surgery	Clamp slipped at operation Presumed implantation	Technical error Recurrence never proven histologically
Male	76	B	Well	11	2·5	0·67	Staple line, pelvic and disseminated peritoneal metastases	Died 1·33 years after surgery	Second adenocarcinoma below main primary tumour cut through This may have seeded to anastomotic leakage cavity	Technical error Defunctioned throughout
Female	61	B	Poor	5	3·0	0·5	Local and metastatic	Died 0·6 years after surgery	Large primary tumour ulcerating anteriorly into the Pouch of Douglas Cleared with a disc of vagina	Aggressive disseminating tumour
Female	81	C	Poor	6	2·0	0·8	Pelvic and hepatic	Died 1·5 years after surgery	Distal mesorectum full of tumour 2 cm below carcinoma	Local recurrence asymptomatic Death metastatic

Discussion

The absence of local recurrence in the group with a margin ≤1 cm is presumed to be due to chance (CI is 0–5·9 per cent compared with 0·8–7·4 per cent in the >1 cm group) The Fisher exact test showed no statistically significant difference in local recurrence rates between these groups.

That those with a margin of >1 cm had significantly less Dukes' A tumours probably results from a technical factor. In low rectal cancer total mesorectal excision and tumour mobilization eventually require that the fingers and thumb compress normal rectum around the tumour and below its palpable lower edge. The clamp is then applied below the fingers. Thus a more solid and bulky tumour tends to result in a larger resection margin.

It may be argued that measurement of the resection margin after fixation of the specimen detracts from these results Williams *et al.*[1]. looked critically at operative specimens and concluded that the effect of fixation was minimal when the resection margins were small. Furthermore, it is the view of the authors that pinning out when the specimen is soft and flexible produces a variable degree of stretching of the tissues.

The idea that a wide margin of normal bowel should be resected distal to a rectal cancer originated from reports by Handley[3] and Cole[4] in 1913 of extensive intramural spread. Grinnell[5] later found distal intramural spread in 12 per cent of his 76 curative anterior resections and became an advocate of the 5 cm rule. Penfold[6] found a downward spread in 8·8 per cent of 546 abdominoperineal excision specimens and reported no 5-year survivors in the group with more than 1 cm spread, despite the maximal distal clearance obtained by abdominoperineal excision. However, Quer *et al.*[7] found distal spread of more than 1·5 cm in only one of 89 curative anterior resections and recommended varying the resection margin with tumour differentiation. Black and Waugh[8] stated that only 2 cm of bowel need be removed distal to the tumour and other authors[9–12] have found no correlation between a smaller distal clearance and local recurrence.

In our experience distal intramural spread below the palpable edge of a rectal cancer is unusual and a sign of very advanced or highly malignant disease. It has not been identified as a cause for local recurrence amongst any patient considered to have undergone a curative operation. Our results[11] strongly suggest that total mesorectal excision combined with routine lavage below a clamp can minimize local recurrence rates to well below 5 per cent, despite drastic reduction of mural margins. Thus a low sphincter-saving anterior resection with a limited resection margin is a viable option which does not compromise the patient's survival prospects

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Announcement

Association of Coloproctology of Great Britain and Ireland

On 9 March 1990 The Association of Coloproctology of Great Britain and Ireland was inaugurated at a meeting at The General Hospital, Birmingham. The objective of this multidisciplinary association is to promote the interests, standards and training in Coloproctology.

The officers of The Association are:

President	G. D. Oates
President-elect	N V. Addison
Honorary Treasurer	R. H. Grace
Honorary Secretary	J. P. S. Thomson
Honorary Assistant Secretary	C G. Marks
Representative on the Presidential Board of Surgical Specialties (Royal College of Surgeons of England)	P. F. Schofield
Representative on the European Council of Coloproctology	R. J. Nicholls

The constitution and an application form (if not attached) may be obtained by writing to the Honorary Secretary, The Association of Coloproctology of Great Britain and Ireland, The Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK.

The Council will be elected by the officers at a meeting on 27 June 1990. The council will then meet in September. The first clinical meeting with the Annual General Meeting will be held during the summer of 1991 It is anticipated that Regional Chapters will be developed during the first year.

Applications for associate membership, membership and senior membership should be made to the Honorary Secretary at the above address as soon as possible so that they will be available for the meeting on 27 June 1990.

Further information may be obtained from James P. S. Thomson, St Mark's Hospital, City Road, London EC1V 2PS, UK; telephone 01-253 1050 ext. 4045.

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Comparison of one dose *versus* three doses of prophylactic antibiotics, and the influence of blood transfusion, on infectious complications in acute and elective colorectal surgery

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In a randomized prospective controlled trial involving 311 patients undergoing acute or elective colorectal surgery, the efficacy and safety of two different single dose and one triple dose regimen of antibiotic prophylaxis, as well as the influence of blood transfusion on postoperative infectious complications, were studied. Postoperative infectious complications occurred in a total of 59 patients (19·0 per cent). There were no major differences between the three treatment groups. Thirty-four patients (10·9 per cent) developed abdominal wound infection, 17 patients (5·5 per cent) intra-abdominal abscess and 16 patients (5·1 per cent) anastomotic leakage. Of 202 patients (65·0 per cent) requiring blood transfusion during hospitalization 57 (28·2 per cent; 95 per cent confidence limits of 23–36 per cent) developed infectious complications, whereas two non-transfused patients (1·8 per cent; 95 per cent confidence limits of 0·2 to 6 per cent; $P<0{\cdot}001$*) developed infectious complications. It is concluded that one single dose of antibiotic prophylaxis in acute and elective colorectal surgery is as protective as a triple dose regimen. The development of infectious complications despite antibiotic prophylaxis is strongly related to blood transfusion.*

Keywords: Prophylactic antibiotic, blood transfusion, postoperative infection, colorectal surgery

Infectious complications contribute greatly to postoperative morbidity. Environmental contamination, the virulence of the microorganisms and the state of host defences are all major determinants of such complications. In colorectal surgery unacceptably high septic complication rates have been described when no antibiotics were used[1]. Bacterial contamination during the operation in such surgery is an important aetiological factor leading to infection. It is well documented that a mixed flora of both aerobic and anaerobic microorganisms will be found in wound sepsis and peritonitis following colorectal surgery[2]. Antibiotic prophylaxis, therefore, must be directed at both types of bacteria[3–7].

Mechanical cleaning of the bowel decreases the risk of bacterial contamination by reducing the quantity of faeces present in the colon at the time of operation[8]. However it has little effect on colonic bacterial count[8]. Oral antibiotics have been shown to be less effective than systemic antibiotics in various studies because of the development of resistant organisms[9,10].

Until 1980 most trials studying prophylaxis in colorectal surgery were conducted with multidose regimens. In recent years more trials have documented that systemic single dose antibiotic prophylaxis in elective colorectal surgery is quite as effective as a multidose regimen[6,11–14] However, there is still some controversy about the ideal regimen and, furthermore, there are only a few prospective studies determining the optimal duration of prophylaxis in acute colorectal surgery[15,16].

Regardless of the use of prophylactic antibiotics it is obvious that infectious complications cannot be completely prevented. In most studies of antibiotic prophylaxis in elective colorectal surgery the frequency of infections varies from 4 to 12 per cent, although higher rates have also been reported[17].

The reason why infectious complications develop despite prophylaxis has been ascribed to factors such as duration of the surgical procedure, contamination of the operative field and nutritional status of the patient. However, in recent studies the use of perioperative blood transfusion has been assigned as an independent risk factor, both for postoperative infectious complications[18,19] and for multiple organ failure[20].

The present study was designed to compare the efficacy and safety of two single dose and one triple dose prophylactic antibiotic drug combination in acute and elective colorectal surgery. Any association between failure of antibiotic prophylaxis and blood transfusion was investigated. This prospective randomized study was carried out in four Danish hospitals (two university hospitals and two county hospitals).

Patients and methods

All patients who underwent acute or elective colorectal surgery between July 1987 and September 1988 were considered for inclusion in the study, which has received the approval of the local Ethical Committee Patients were excluded if they had any of the following (1) a history of sensitivity to any of the antibiotics used, or a history of receiving antibiotics within 2 days of operation, (2) age less than 18 years, (3) radiation injury of the colon or rectum; (4) diffuse peritonitis, (5) York-Mason's operation or (6) ileo–anal reservoir

Stratification and randomization

With informed consent, patients were stratified into acute or elective colorectal surgery. After stratification all patients were randomly allocated using sealed envelopes to one of three treatment groups (A) cefuroxime 3 g and metronidazole 1500 mg intravenously after induction of anaesthesia, (B) ampicillin 3 g and metronidazole 1500 mg intravenously after induction of anaesthesia or (C) ampicillin 1 g and

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metronidazole 500 mg intravenously after induction of anaesthesia and repeated 8 and 16 h later

Mechanical bowel preparation

In patients undergoing elective operation the bowel was emptied following the normal procedure of the participating department. This was either with oral laxative and saline enema, or by whole gut irrigation. No bowel preparation was used in patients undergoing acute operation. No oral antibiotics were given Surgeons assessed the effectiveness of bowel preparation by the amount of faecal loading at the time of operation.

Operative technique

All anastomoses were done in two layers by an open technique ($n=157$) or with an intraluminal stapling device ($n=54$) Intraperitoneal drains, if used, were tube drains brought out through separate incisions Subcutaneous drains were not allowed. After abdominoperineal excision the perineal wound was sutured primarily, and the pelvic cavity was drained through either a suprapubic suction drain brought out via a separate incision or a suction drain brought out through the perineal wound All participating surgeons were consultants or senior registrars

Intraoperative observations

The procedure, its duration and blood loss were recorded, as were intraoperative, pre-, and postoperative blood transfusions.

Postoperative observations

Follow-up examination included regular wound inspection from the third postoperative day until stitch removal or patient discharge. All wounds were reviewed by an independent assessor. All patients were followed up in the out-patient clinic for 30 days after operation If they failed to attend, they were contacted by telephone.

Abdominal and perineal wound infections were defined as accumulations of pus, either with spontaneous discharge or requiring surgical drainage Material from infected wounds was cultured both aerobically and anaerobically. Wounds with serous discharge resulting in positive bacteriological culture, and wounds with serous or purulent discharge after return home, were included in the infected group. Deep surgical sepsis consisted of (1) intra-abdominal abscesses defined as an intraperitoneal or pelvic collection of pus diagnosed by ultrasonography, laparotomy or spontaneous discharge; (2) anastomotic leakage diagnosed by fever and faecal fistula or peritonitis; and (3) septicemia defined as the presence of spiking fever associated with positive blood cultures. Other surgical complications such as abdominal wound dehiscence, bleeding and ileus were considered separately.

Pneumonia was diagnosed by fever and infiltrate on chest radiograph. Urinary tract infection was diagnosed when symptoms were present and culture yielded more than 100 000 pathogens per ml.

No postoperative administration of antibiotics was allowed unless a documented secondary infection was present All such findings were recorded.

Postrandomization exclusion

Patients in whom the protocol was violated during operation were excluded from evaluation, as were patients who died within 7 days of operation without signs of infectious complications.

Statistical analysis

Differences between groups were tested using the χ^2 test or Fisher's exact test (for numbers below 60). The variables of patients who developed infectious complications were compared with those of patients without infectious complications using the χ^2 test or Student's t test or, for numbers not normally distributed, the Mann–Whitney U test. Results were considered significant at $P<0\cdot05$ (95% confidence limits for differences were calculated) A multivariate stepwise logistic regression analysis was used to identify independently significant factors for use in predicting infectious complications.

Results

A total of 441 patients underwent colonic and rectal procedures at the four hospitals during the study period. In 104 patients, randomization was not performed because of exclusion criteria: no informed consent ($n=19$); history of sensitivity to one of the antibiotics ($n=21$); antibiotics within 2 days of operation ($n=14$); radiation injury ($n=10$); diffuse peritonitis ($n=12$); ileo–anal reservoir ($n=25$); York-Mason's operation ($n=2$); less than 18 years of age ($n=1$).

Of the 337 patients who entered the study (287 for elective operations and 50 for acute operations) 26 (15 elective and 11 acute) were withdrawn. The reason for withdrawal was violation of the protocol in 20 patients; abdominal exploration without resection ($n=15$) and diffuse peritonitis diagnosed at operation ($n=5$). Six patients died within 7 days because of myocardial infarction ($n=1$), pulmonary embolus ($n=1$) or cardiopulmonary insufficiency ($n=4$).

In total 311 patients, 272 undergoing elective surgery and 39 undergoing acute surgery, were suitable for evaluation and analysis, and 107 were allotted to group A, 100 to group B and 104 to group C. The randomized groups were well matched (*Tables 1* and *2*). In acute operations the diagnosis was malignancy in 30, diverticular disease in five and miscellaneous in four patients.

Postoperative infectious complications

Postoperative septic complications related to the surgical procedure developed in 59 patients (19·0 per cent). In patients undergoing acute surgery 14 (36 per cent; 95% confidence limits of 21 to 53 per cent) developed septic complications whereas 45 (16·5 per cent; 95% confidence limits of 12·to 20 per cent, $P<0\cdot01$) undergoing elective surgery developed septic complications (*Table 3*). Nineteen patients developed two or more infectious complications (ten patients had both anastomotic leakage and intra-abdominal abscess) and the total number of complications was 81. In patients with anastomotic leakage, the anastomosis had been stapled in five and handsewn in 11 ($P>0\cdot05$), and in patients with intra-abdominal abscesses the anastomosis had been stapled in three and handsewn in 14 ($P>0\cdot05$). Considering elective operations, there were no differences in septic complications between the three treatment groups. In acute operations, one patient in group A developed abdominal wound infection (6 per cent, 95% confidence limits of 0 to 30 per cent) whereas six patients in group B developed wound infection (55 per cent; 95% confidence limits of 23 to 83 per cent; $P<0\cdot05$) Four patients in group C (33 per cent) developed wound infection ($P>0\cdot05$). There were no differences in the other septic complications between the three treatment groups.

Microorganisms

Pathogenic microorganisms were isolated in 29 (85 per cent) of the 34 patients with abdominal wound infections. The commonest were *Escherichia coli* (15 patients), *Streptococcus faecalis* (7 patients), enterobacteriacea (6 patients), *Proteus* species (4 patients), *Pseudomonas aeruginosa* (4 patients) and *Klebsiella* species (3 patients). In eight patients infected with *E. coli*, resistance to ampicillin was recorded No resistance to cefuroxime was recorded.

Table 1 *Demographic and clinical characteristics of the patient groups*

	A	B	C
No of patients	107	100	104
Median age in years	66	64	66
(range)	(18–86)	(18–90)	(26–90)
Male/female	53/54	49/51	54/50
Median weight in kg	65	67	67
(range)	(34–121)	(41–111)	(41–103)
Diabetics	3	4	5
Elective operations	91	89	92
Acute operations	16	11	12
Diagnoses			
Malignancy	79	75	87
Benign polyps	1	0	3
Diverticular disease	8	9	6
Inflammatory bowel disease	8	7	4
Miscellaneous	11	9	4

Table 2 *Surgical characteristics of the patient groups*

	A		B		C	
	Elective	Acute	Elective	Acute	Elective	Acute
Ileocolostomy	4	1	2	0	2	1
Right hemicolectomy	16	3	14	2	15	1
Left hemicolectomy	2	1	1	0	4	1
Sigmoid resection	14	2	13	2	23	2
Anterior resection	1	1	6	0	6	0
Low anterior resection	11	0	9	0	7	0
Other resections	5	1	4	0	4	1
Colostomy	6	4	5	1	5	4
Hartmann's excision	9	3	6	6	7	2
Colorectal anastomosis*	4	0	11	0	3	0
Colectomy and ileostomy	2	0	4	0	1	0
Total colectomy	2	0	1	0	1	0
Closure of colostomy	3	0	3	0	5	0
Abdominoperineal resection	12	0	10	0	9	0

*Colorectal anastomosis is restoration of continuity of the bowel following a Hartmann's procedure

Table 3 *Septic complications*

	Acute surgery	Elective surgery	*P*
No. of patients	39	272	
Abdominal wound sepsis	11(28)	23(8·5)	<0·001
Perineal wound sepsis	–	8(22·8)	
Intra-abdominal abscess	5(13)	12(4·4)	<0·05
Anastomotic leakage	3(16)	13(6·8)	
Septicaemia	2(5)	4(1·5)	

Values in parentheses are percentages

Table 4 *Comparisons of infected and uninfected patients in colorectal surgery*

	Infected	Uninfected	*P*
No. of patients	59	252	
Median age in years (range)	67 (37–81)	65 (18–90)	
Male/female	28/31	128/124	
Median weight in kg (range)	69 (42–121)	66 (34–112)	
Diabetics	4	8	
Admission haematocrit	0·37	0·39	
Diagnoses			
Malignancy	46	195	
Benign polyps	1	3	
Diverticular disease	8	15	<0·05
Inflammatory bowel disease	2	17	
Miscellaneous	2	22	
Drainage of abdominal cavity	32	96	<0·05
Assessment of bowel content			
Clean bowel	35	200	
Faecal loaded bowel	9	34	
Faecal loading of the abdominal cavity	15	18	<0·05
Duration of surgery > 180 min	19	71	

Table 5 *Infectious complications, blood transfusions and intraoperative blood loss*

	Infected	Uninfected	*P*
No. of patients	59	252	
Transfused patients†			
Preoperative	13	19	<0·001
Intraoperative	51	100	<0·001
Postoperative	25	61	<0·01
Total	57	145	<0·001
*Number of transfusions (units)‡			
Preoperative	2(1–10)	2(1–4)	
Intraoperative	4(1–13)	2(1–20)	<0·05
Postoperative	3(1–10)	1(1–3)	<0·05
Overall	5(1–13)	2(1–20)	<0·05
*Intraoperative blood loss (ml)			
Transfused patients	570(100–2000)	551(0–9000)	
Non-transfused patients	450(400–500)	250(0–600)	

*Values given are numbers or median(range) †χ^2-test and ‡Mann–Whitney *U* test are used for statistical analysis

Comparison of patients with and without infectious complications

Univariate analysis comparing patients who developed infectious complications with uninfected patients revealed significantly more infections in patients with diverticular disease (*Table 4*). Four of the patients with diverticular disease and infections had emergency surgery because of diverticulitis and obstructive colonic ileus. With respect to the other data there were no differences between acute and elective operations. None of the surgical procedures were specifically associated with a high frequency of infectious complications. Drainage as well as faecal loading of the abdominal cavity were related to a high risk of septic complications (*Table 4*). Faecal loading of the abdominal cavity in 33 patients was followed by fourteen instances of abdominal wound sepsis, three anastomotic leaks, and two intra-abdominal abscesses.

Patients with operative procedures lasting more than 180 min had no greater risk of developing infectious complications than patients undergoing shorter procedures (*Table 4*). The longer operations were colectomy (total or with ileostomy), abdominoperineal resection and colorectal anastomosis. In abdominoperineal resection or total colectomy, four of 13 patients with drainage through the sutured perineal wound developed perineal wound infection, whereas four of 22 patients with suprapubic drainage developed such infection ($P > 0·05$).

Two-hundred and two patients (65 per cent) required blood transfusions during hospitalization (*Table 5*). There were no differences in the administration of transfusions between the acute and elective groups. Fifty-seven transfused patients (28·2 per cent; 95% confidence limits of 23 to 36 per cent) and two non-transfused patients (1·8 per cent; 95% confidence limits of 0·2 to 6 per cent) developed septic complications ($P < 0·001$).

Table 6 *Multivariate analysis of individual risk factors with infectious complications as the dependent variable*

Risk factor	χ^2	P	Degrees of freedom
Age	0·35	0·560	1
Sex	<0·01	0·990	1
Weight	0·43	0·514	1
Haematocrit	4·98	0·026	1
Emergency surgery	6·60	0·010	1
Type of operation	18·21	0·157	13
Duration of surgery	0·71	0·400	1
Drainage	1·75	0·190	1
Faecal loading of the abdominal cavity	5·12	0·024	1
Estimated blood loss	0·12	0·733	1
Blood transfusions	23·79	<0·001	1

The excess risk of infectious complications in patients receiving blood transfusions was, therefore, 26·4 per cent.

The overall number of blood transfusions in patients developing infectious complications significantly exceeded the number of transfusions in patients without complications (*Table 5*). The administration of blood was associated with low admission haematocrit; 0·35 in transfused patients *versus* 0·39 in non-transfused patients ($P<0·05$). However, the intraoperative estimation of blood loss was similar in all transfused patients, although a single patient bled 9000 ml. Among the remainder the highest blood loss was 3100 ml and 11 patients bled between 2000 and 3100 ml.

When independent variables were combined in the multiple stepwise logistic regression (*Table 6*), only four factors had significance in terms of predicting infectious complications: emergency surgery, faecal loading of the abdominal cavity, haematocrit and blood transfusion. However emergency surgery, faecal loading of the abdominal cavity and haematocrit were related to infectious complications concomitant with blood transfusion. In emergency surgery 56 per cent of the transfused patients developed infections whereas there were no infective complications in the non-transfused patients. In patients with faecal loading of the abdominal cavity only those who received blood transfusion (15 out of 20 patients) developed septic complications. Thirteen patients received no transfusions and developed no complications.

Postoperative infections not directly related to surgery

Twenty-seven patients (8·7 per cent) had postoperative urinary infections and 18 (5·8 per cent) developed pneumonia. These complications were evenly distributed in the three treatment groups and all resolved after intravenous or oral antibiotics. Of 148 patients with a central venous catheter one patient developed catheter sepsis.

Complications of antibiotic use

Only one adverse reaction was reported, a true anaphylaxis with cardiac arrest after intravenous injection of ampicillin in a group B patient. The patient was resuscitated and there were no late complications.

Reoperations not related to infectious complications

In eight patients (2·6 per cent) a dehiscence of the abdominal fascia was resutured without the use of any antibiotic regimen. One of these patients developed a deep wound infection 10 days after resuture. Reoperation because of ileus was carried out in four patients. One patient had further surgery for pulmonary embolism and one for an arterial embolism in the leg.

Postoperative mortality

A total of 20 patients (6·4 per cent) died in a median of 15 (8–30) days after surgery. Seven patients (18 per cent) undergoing acute surgery died and 13 patients (4·8 per cent) undergoing elective surgery died ($P<0·01$). Two patients (one acute and one elective) died of infectious complications with sepsis and multiple organ failure. Both belonged to group B. The other causes of death were cardiopulmonary insufficiency in 13 patients, disseminated cancer in three patients, myocardial infarction in one patient and pulmonary embolism in one patient. There were no statistically significant differences between the treatment groups.

Discussion

This study has shown that in colorectal surgery septic complications cannot be completely prevented, despite the use of prophylactic antibiotics. Following emergency surgery 36 per cent of patients developed septic complications and following elective surgery 17 per cent of patients developed septic complications. The study was carried out without including a non-treated control group because there is no longer any ethical basis for conducting trials in major colorectal surgery with a placebo arm[1]. Except for two, all patients who developed infectious complications received blood transfusion either before, during or after operation.

The aim of this study was to compare the prophylactic effect of a single dose *versus* a triple dose of identical antibiotics as well as to compare two different single dose regimens. Metronidazole was used in all three regimens as the antianaerobe agent. It was combined with one or three doses of ampicillin or with one dose of cefuroxime. Ampicillin had been widely used in Scandinavia in colorectal surgery, especially in combination with metronidazole, and in some studies has reduced the incidence of wound infection in elective colorectal surgery to about 5–6 per cent[12,21]. Furthermore, the administration of ampicillin was based on our knowledge of the sensitivity of the predominant organisms isolated from previous infections after colorectal surgery in the participating hospital departments[5]. Cefuroxime was chosen as an alternative agent because of its superior effect on coliform bacteria, which can be achieved in serum and tissue by a single intravenous dose of 1·5 g[7]. In an attempt to ensure a prolonged effect of the single dose regimen, both cefuroxime and ampicillin were given intravenously in doses of 3 g.

The incidence of the postoperative septic complications in the present study was equivalent to results from most other studies considering both elective[4,10,12,13,22,23] and acute[15,16] surgery. Only 12·5 per cent of all the operations were acute. A decrease in frequency of acute operations has been emphasized by others[24], and has been attributed to more strict indications for operation. For example investigation of patients with mechanical bowel obstruction has been improved thereby avoiding unnecessary acute operations.

The reasons for the marked difference in occurrence of wound infection and intra-abdominal abscesses between emergency and elective operations is not obvious. In acute surgery, neither faecal loading of the abdominal cavity or duration of surgery could be assigned as factors responsible for more infections than in elective surgery. The emergency group received no more blood transfusions than the elective group. The predisposition of diverticulitis to cause postoperative infectious complications has previously been described[15], and in the present study four of five patients with acute diverticulitis and obstruction developed infections. However, the sample size in acute surgery was very small and no worthwhile conclusions can be drawn.

The three prophylactic treatment regimens were effective in all kinds of surgery. The high incidence of perineal wound infection after abdominoperineal excision is a well-known complication[12,23,25]. The incidence of resistance to ampicillin in 50 per cent of patients infected with *E. coli* indicated that, in our environment, the pattern of sensitivity to ampicillin has changed recently. The development of resistant strains may very well be accompanied by an increase in infectious complications, and weakens the conclusions relating to other causes of infections.

The development of intra-abdominal abscesses in a total of 17 patients (5·5 per cent) may have been due to anastomotic leakage in ten of these patients. It is difficult to know whether lack of antibiotic cover may lead to septic complication secondary to anastomotic leakage or whether anastomotic leakage by itself is the primary reason for the development of intra-abdominal abscesses. There was no difference in the frequency of anastomotic leakage between stapled and handsewn anastomoses. The technique of anastomosis is, however, important in preventing infectious complications. Both experimental[26] and clinical studies[6,27–29] have shown that leaking intestinal content, when creating the anastomosis, is a significant risk factor for developing postoperative infectious complications. In the present study the bowel was clean in 69 per cent with anastomotic leakage. In only three patients was leaking of intestinal content observed, indicating that other factors influence anastomotic healing. Besides appropriate perioperative antibiotics which may prevent localized serosal abscesses[26], the degree of tension, blood supply and blood transfusion during operation may influence healing[28].

Failure of the antibiotics to control postoperative infectious complications in 19 per cent of patients may be attributed mainly to the use of blood transfusion. Furthermore, in transfused patients, low admission haematocrit, acute surgery, and faecal loading of the abdominal cavity, were additional risk factors. Eliminating these risk factors may eliminate infectious complications. Transfusion was associated with all the infectious complications independent of patient age, type of operation and duration of surgery. These results are in accordance with the elective colorectal cancer surgery results published by Tarrter[19]. Dawes *et al.*[30] also documented that blood transfusion was a good indicator of the risk of infection after penetrating abdominal injury.

It has previously been claimed that infectious complications are more frequent when the operative procedure exceeds 4 h[31], and association between type of operation and rate of infection has been described[32] We found no difference in infections between patients having their surgical procedure completed within 3 h and those with procedures of 3 h or more. Considering only transfused patients, the type of operation did not influence the frequency of infection at all.

The significant relation between the development of postoperative infectious complications and blood transfusion was independent of the timing of transfusion, as all transfused patients were in a higher risk class than non-transfused patients. Like others[18,28] we found that infected patients received more transfusions than transfused patients without infections However, it was surprising that the blood loss in infected and uninfected patients receiving blood transfusions was similar. The indications for intraoperative blood transfusion, therefore, seem moot and the contribution of blood transfusion to infectious complications cannot be attributed simply to those conditions requiring transfusion The relationship of admission haematocrit and pre- and postoperative blood transfusion to infectious complications, however, indicated that the severity of the disease and underlying medical condition may reflect the need for transfusion. Unfortunately we did not prospectively record tumour size, tumour differentiation and Dukes' classification which also may have reflected a need for transfusion.

The effect of blood transfusion on infectious complications may be explained by immunological suppression The immunosuppressive effect of perioperative blood transfusion has been investigated retrospectively in several papers, many of which affirmed a relationship between perioperative blood transfusion and recurrence of malignant disease[33]. However, in a recent review[34], it was emphasized that definitive conclusions cannot yet be drawn. In a prospective study Tartter *et al.*[35] found that in patients with inflammatory bowel disease perioperative blood transfusion was followed by prolonged depression of the peripheral lymphocytes and T cells. These observed alterations in immune function may also have significance when related to infections. It is well established in anergic patients that the depleted immune response leads to a considerable risk of developing postoperative infectious complications[36,37]. We cannot draw any conclusions about the immunological status of the patients in the present study, but it is possible that the occurrence of infectious complications in transfused patients may be due in part to immunosuppression.

In 1968 Simmons *et al.*[38] suggested that haemoglobin interfered with the escape of *E. coli* from the peritoneal cavity, allowing time for lethal levels of endotoxin to accumulate. We found that in patients with faecal loading of the abdominal cavity only those who were transfused developed infectious complications. Increasing faecal contamination probably depresses the ability of the host to confront the bacterial load successfully[38].

In conclusion, one single peroperative dose of antibiotic prophylaxis in acute and elective colorectal surgery is sufficient. The antibiotic prophylaxis should be directed against both aerobic and anaerobic microorganisms. However, when selecting antibiotics against aerobic organisms, the marked increase of ampicillin resistant bacterial strains must be taken into consideration. The present analysis has demonstrated that the likelihood of developing infectious complications after colorectal surgery is related to the use of blood transfusion. Admission haematocrit, acute operations and faecal loading of the abdominal cavity were additional risk factors. At present there is no need for further studies comparing different antibiotics in the prevention of postoperative infectious complications in colorectal surgery. It is of greater importance in clinical trials to study the immunosuppressive effect of blood transfusion in the hope of reducing immunosuppression, and to consider the potential clinical value of adoptive immunotherapy.

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Effect of postanal repair on progress of neurogenic damage to the pelvic floor

Physiological evaluation of the anorectum and pelvic floor muscles was carried out in 18 patients before and 9–35 months after postanal repair for anorectal incontinence. Thirteen patients (72 per cent) were improved, but in these patients the fibre density in the external anal sphincter muscle and the pudendal nerve terminal motor latency were both increased after surgery. In the five patients not improved after surgery only a few unstable motor unit potentials could be recorded in the external anal sphincter muscle. In two of these patients the pudendal nerve terminal motor latency could not be recorded after surgery. We suggest that this progression in the neurogenic damage to the pelvic floor muscles after postanal repair may be caused by the operation, and that it may be responsible for the poor functional outcome noted in some patients.

Keywords: Postanal repair, anorectal incontinence, anorectal physiology, anal sphincter, electromyography

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In patients with idiopathic anorectal incontinence there is weakness of the smooth and striated anal sphincter muscles, shown by decreases in the resting and squeeze anal pressure measurements, increases in the anorectal angle and abnormal perineal descent[1–4]. Histological[5,6] and electrophysiological investigations have shown that in the majority of these patients there is damage to the innervation of the striated anal sphincter musculature, with an increase in the mean pudendal nerve terminal motor latency[7,8] and an increase in the fibre density in the external anal sphincter and puborectalis muscles[9–11]. The postanal repair operation was devised by Parks[12] to relieve anorectal incontinence by tightening the pelvic floor musculature and the external anal sphincter, and so restoring the anorectal angle and anal sphincter integrity. Although postanal repair is helpful in more than 60 per cent of patients operated on[13–17], the factors which make the operation successful in some patients but not in others are not understood.

The aim of the present study was to investigate the effect of postanal repair on the striated anal sphincter muscles and their innervation (using electrophysiological tests and anorectal manometry) and to relate the findings to the surgical result.

Patients and methods

Patients

A postal questionnaire was sent to the 34 patients (all women, aged 38–77 years; mean 65 years) treated by postanal repair for anorectal incontinence at St Mark's Hospital during the 2-year period 1984–1986. None had peripheral neuropathy, diabetes mellitus, spinal cord disease or other neurological disorder. Twenty-eight patients answered the questionnaire, and 18 of these agreed to come to the laboratory for repeat anorectal physiological studies. Of the remaining six patients, one had died and two proved untraceable. All 34 patients had been incontinent to solid stool with severe soiling for at least 9 months before operation (range from 9 months to 20 years). Of the 18 patients who returned for anorectal physiology studies, one had had surgery for complete rectal prolapse but remained incontinent 18 months before postanal repair, and in one patient incontinence had followed an anal stretch. In all these 18 patients the preoperative anorectal physiological studies had revealed a neurogenic cause for faecal incontinence with a poor squeeze anal pressure, an increased fibre density in the external anal sphincter muscle, and/or an increased pudendal nerve terminal motor latency. The postoperative physiological investigations were carried out 9–35 months after postanal repair.

The questionnaire assessed the outcome of surgery in terms of continence to flatus, liquid stools and mucus, and solid stool. The surgical result was classified as: good (continent after surgery with no or only minor soiling), fair (improved but still with some incontinence to liquid or poorly formed stool); and poor (no improvement or worse). After the physiological investigation the questionnaire was reviewed with the patient to ensure accuracy of responses.

Anorectal physiology

The same physiological investigations were performed at the follow-up examination as at the initial evaluation. These consisted of the standard programme of investigations that have been developed at St Mark's Hospital[7–10,18]. All the postoperative investigations were carried out by one of the authors (S.L.), and informed consent was obtained according to guidelines approved by the St Mark's Hospital Ethical Committee. The preoperative investigations had been performed in the laboratory at St Mark's Hospital by two other investigators. These investigators' technique and their reliability had previously been validated in relation to the normal values reported from our laboratory[19,20]. The following tests were carried out.

Anal manometry. The maximal resting anal pressure and the maximal squeeze pressures were determined with a small, water-filled balloon, connected to a pressure transducer, using the method described previously from this laboratory. In a group of normal subjects the resting anal pressure ranged from 60 to 100 cmH$_2$O, and during maximal squeeze contraction of the anal canal this pressure doubled[9,19,20].

Perineal descent. The position of the anal verge relative to the ischial spine was measured at rest and during a maximal straining effort using the St Mark's perineometer[16]. In a group of 103 normal subjects the mean(s.d.) position of the perineum at rest was 2·5(0·6) cm above the level of the ischial tuberosities, during a straining effort it lay a mean(s.d.) distance of 1·6(0·3) cm above this transischial plane[18].

Pudendal nerve studies. The left and right pudendal nerve terminal motor latencies (PNTML) were measured from recordings of the muscle action potential evoked in the external anal sphincter muscle after supramaximal stimulation of the pudendal nerves transrectally, using the St Mark's disposable pudendal electrode (Dantec 13L40, Bristol, UK). In a group of normal subjects the mean(s.d.) PNTML was 2·0(0·2) ms[7,8,19,20].

Single fibre electromyography. Twenty consecutive motor unit potentials were recorded from the two sides of the external anal sphincter muscle during spontaneous activity of this muscle using the

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standard methodology of single fibre electromyography (EMG). The mean number of spike components in these potentials is the fibre density, an index of the packing density of muscle fibres making up individual motor units in the muscle. In a group of normal subjects the mean(s.d.) fibre density in this muscle was 1·5(0·16)[9,10,19,20].

Statistical methods

The Wilcoxon rank sum test for paired and unpaired samples was used for comparison between groups. Differences were considered significant when $P<0{\cdot}5$.

Results

Outcome of surgery

Of the 28 patients who answered the questionnaire, 21 (75 per cent) were improved after postanal repair. Nine described a good result and 12 a fair result. The outcome was poor in 7 patients, and one of the latter was worse after the operation. Of the 18 patients who attended for repeat anorectal physiology studies 13 (72 per cent) were improved after postanal repair (five of whom had a good result and eight a fair result) and in five the outcome was poor. Thus the patients returning for repeat anorectal physiology studies had similar results from surgery when compared with those who did not. The 18 patients who were studied for a second time were divided, for the purposes of this study, into a group of 13 improved patients and a group of five in whom surgery had failed (*Figures 1–5*).

Anal manometry

Anal manometry was carried out in all the 18 patients studied both before and after surgery. The mean resting anal pressure (*Figure 1*) increased from 42 cmH_2O before operation to 60 cmH_2O after operation ($P<0{\cdot}01$). However, in the 13 improved patients the mean resting anal pressure showed no significant increase (38 cmH_2O before operation and 49 cmH_2O after operation), although in the five unimproved patients the mean resting anal pressure increased from 50 to 88 cmH_2O ($P<0{\cdot}01$).

The mean squeeze anal pressure (*Figure 2*) showed no significant increase (52 cmH_2O before operation to 59 cmH_2O after operation) in the patients who improved after postanal repair, but in the five patients who were not improved after surgery the mean squeeze anal pressure was lower (6 cmH_2O) after surgery than before (33 cmH_2O; $P<0{\cdot}01$). After surgery the mean squeeze anal pressure was significantly greater in the improved patients than in the failed group ($P<0{\cdot}01$). Before surgery there was no significant difference in the mean squeeze anal pressures in the two groups.

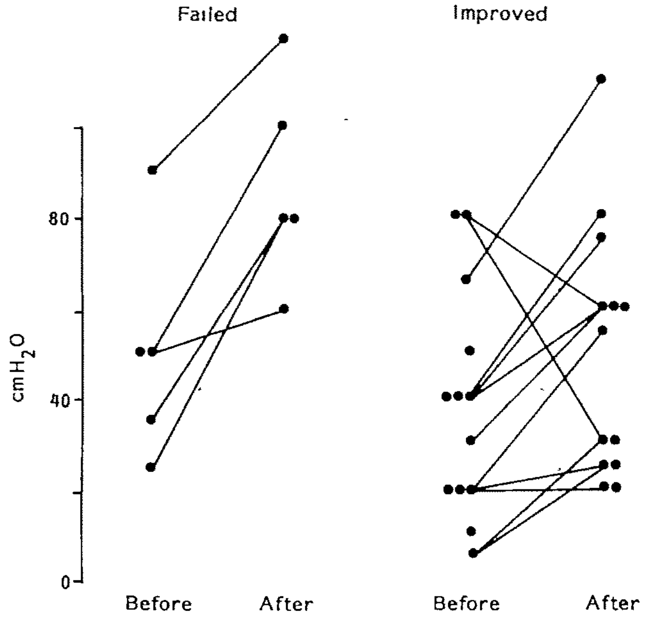

Figure 1 *Resting anal pressure measurements before and after postanal repair in patients who were improved and in those who were not helped (failed) by this operation. All the 18 patients were studied before and after surgery*

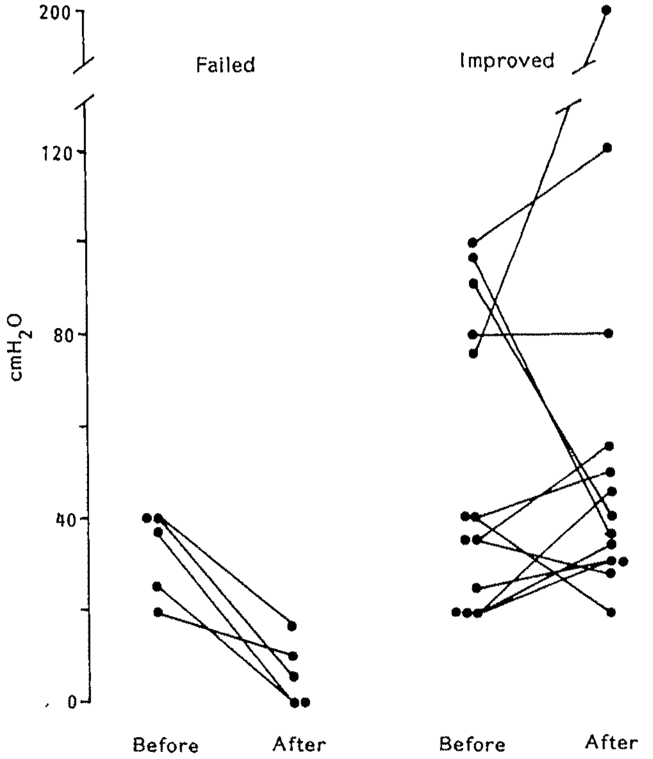

Figure 2 *Squeeze anal pressures in the failed and improved patient groups; the squeeze anal pressure represents the maximal pressure during voluntary contraction minus the maximum resting anal pressure. In the failed group the squeeze anal pressure was reduced after the operation. All the 18 patients were studied before and after surgery*

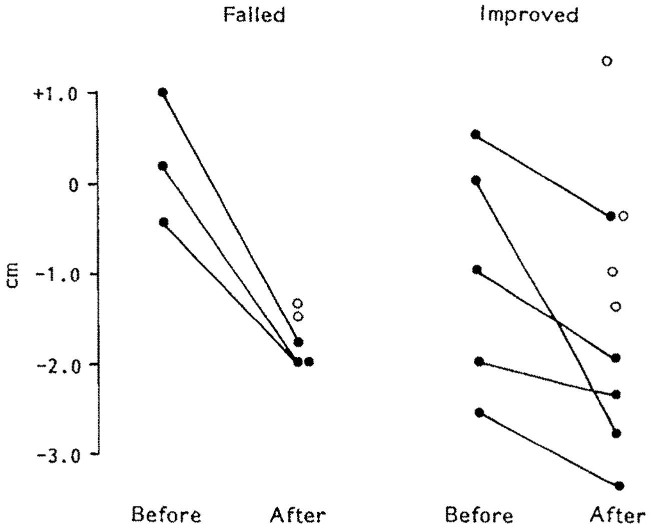

Figure 3 *Postanal repair was followed by a lower position of the perineum during straining with respect to the plane of the ischial tuberosities in both groups of patients. This investigation was carried out before and after operation in only eight of the 18 patients available for study. The open symbols represent patients studied only once*

Perineal descent

Incomplete data were available. The resting perineal position was recorded in six patients before surgery, three of whom were improved and three unimproved after postanal repair. In these six patients the resting perineal plane was lower after surgery; the mean resting position before surgery was 0·8 cm above the

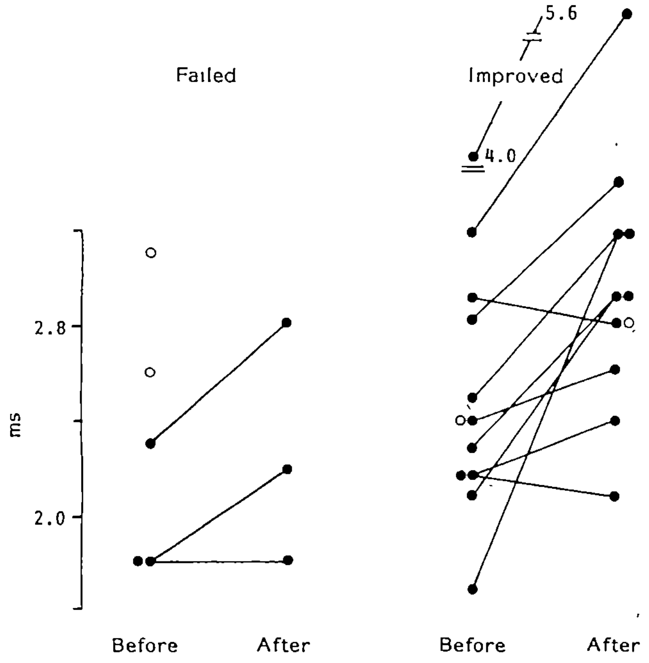

Figure 4 *The pudendal nerve terminal motor latency (PNTML) was increased after postanal repair. The open symbols in the failed group represent patients in whom the PNTML could not be recorded on either side postoperatively, and these symbols in the improved group represent patients studied only once*

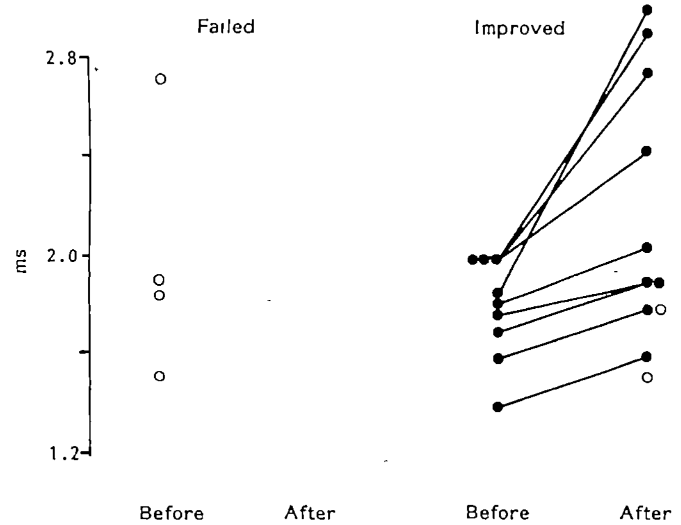

Figure 5 *The single fibre EMG fibre density was increased after postanal repair. In the patients in whom the operation failed to alleviate faecal incontinence too few motor unit potentials could be recorded for calculation of fibre density (see text) indicating a marked loss of functioning motor units in these muscles. The open symbols in the improved group represent patients studied only once*

transischial plane, and after surgery it was 1·0 cm below this plane ($P<0{\cdot}05$).

The position of the perineal plane during a maximal straining effort (*Figure 3*) was measured both before and after surgery in eight patients, five of whom were improved and three unimproved. In these eight patients the perineal plane during straining was lower after postanal repair (mean position 1·7 cm below the transischial plane) than before surgery (mean position 0·5 cm below the transischial plane; $P<0{\cdot}01$). The numbers of observations in the two groups of patients were too small for statistical testing.

Pudendal nerve terminal motor latencies

There was no significant difference between the mean preoperative PNTML in the improved (2·25 ms) and unimproved patients (2·55 ms). Eleven of the 13 patients who improved after postanal repair had PNTML measurements made both before and after surgery. The mean PNTML in these patients increased from 2·4 ms before operation to 3·0 ms after surgery ($P<0{\cdot}05$). In the patients who failed to improve after postanal repair the PNTML was increased in two of the three patients in whom it proved possible to record it after operation (*Figure 4*). In the other two failed patients no PNTML could be recorded on either side after operation. One patient in the improved group did not wish to have this investigation repeated, and in another it had not been carried out before operation.

Single fibre electromyography

The fibre density had been measured in 12 of the 18 patients before operation, eight of whom were improved and four unimproved (*Figure 5*). There was no significant difference between the fibre density in these two groups of patients before postanal repair. In the eight patients who improved after the operation the fibre density was greater after operation (mean 2·31) than before operation (mean 1·79; $P<0{\cdot}01$). In the four patients who were not improved by postanal repair the fibre density could not be calculated after operation because less than five unstable motor unit potentials could be recorded in the external anal sphincter muscle in these patients, despite a careful search of the muscle with the recording electrode. Three patients who had not had single fibre EMG carried out before operation did not wish to have this investigation after operation.

Discussion

Several surgical groups have noted that Parks' postanal repair[12] is effective in the management of idiopathic neurogenic anorectal incontinence in only about two-thirds of patients operated upon[13–17,21]. The operation was designed to restore faecal continence by decreasing the abnormally obtuse anorectal angle found in patients with idiopathic anorectal incontinence, thus improving the functional competence of the anal sphincter mechanism and increasing the length of the anal canal. These aims are usually achieved in patients in whom the outcome is successful[13]. Miller *et al.*[16] found that there was an increase in resting and squeeze anal pressure after successful postanal repair, although they found no consistent change in the anorectal angle. However, Keighley and Fielding[21] found no change in maximal squeeze pressure in the anal canal after postanal repair, and Womack *et al.*[17] reported no change in either maximal squeeze pressure or anorectal angle in their patients with a successful outcome after postanal repair, although they noted a significant increase in the length of the anal canal. We found no consistent change in resting or squeeze anal pressure measurements after postanal repair in patients who improved but, in those who did not improve, the resting pressure was increased and the squeeze pressure reduced after the operation (*Figures 1* and *2*). An increase in resting pressure in the anal canal after postanal repair is probably due to local mechanical changes such as fibrosis, rather than to a direct effect of the operation on the internal anal sphincter itself[13,17].

Our electrophysiological investigations have revealed increased neurogenic damage to the striated sphincter musculature after postanal repair, even in patients who were functionally improved. In patients who were not improved, or who deteriorated after the operation, we found a marked increase in the neurogenic abnormality shown by the presence of only a few isolated, unstable motor unit potentials in the external anal sphincter muscle. In addition, the PNTML was markedly increased after operation, even in patients who improved, and could not be recorded in some of those who did not. This is unlikely to be due to technical factors[19,20,22].

Although only 18 of the 34 patients we contacted returned for postoperative anorectal physiology studies, there was no difference in the surgical outcome between those we studied and those we did not, suggesting that selection bias was not a factor in our results.

The natural history of neurogenic anorectal incontinence is for the functional disorder to progress slowly during many years, rather than for any sudden deterioration to develop. However, formal longitudinal anorectal physiology studies to document the rates of change in these variables are not available. Our results suggest that postanal repair may accelerate neurogenic damage to the pelvic floor striated sphincters. This could arise from trauma to the innervation of the pelvic floor musculature during the operative dissection, or by entrapment of the pudendal nerves in fibrous tissue. In addition, increased perineal descent would itself exacerbate the stretch-induced damage that seems to occur during straining at stool[22].

The relatively small number of patients we have studied precludes consideration of those features in the preoperative investigations that might predict the result of postanal repair but, clearly, this is an important problem for further study.

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Faecal occult blood testing in symptomatic patients: comparison of three tests

This study examines three faecal occult blood tests, Haemoccult®, Fecatwin® and E-Z Detect®, each with different sensitivities, to determine which is best suited for use in symptomatic patients – both for the detection of cancer and of non-malignant mucosal disease of the large bowel. A test was completed by 1025 patients before double-contrast barium enema and the performance of each test was determined from the result of this investigation. The study was completed by 969 patients. There were 49 patients with colorectal cancer, 92 patients with a cancer or a polyp >5 mm, and 130 with some mucosal abnormality. The test most sensitive for blood, Fecatwin, detected 14 of 15 (93 per cent) cancers and 29 (69 per cent) of 42 patients with mucosal disease (including inflammatory bowel disease) but gave three times as many false positive results as the Haemoccult test, which is less sensitive for blood. The chance of a patient with a positive Haemoccult result having mucosal disease on barium enema was 24 of 47 patients (51 per cent) (two-thirds of these having colorectal cancer). A negative Haemoccult result, however, was unreliable and should not influence patient management. A test less sensitive for blood than Haemoccult was found to be of little value in symptomatic patients.

Keywords: Colorectal disease, symptoms, faecal occult blood test

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Most clinically significant disease of the large bowel affects the mucosa and could give rise to occult bleeding. The symptoms in many of these diseases are similar and are also found in less serious colonic disorders (for example, diverticular disease) or anorectal conditions. A faecal occult blood test would be of use in patients with symptoms of large bowel disease if it could identify those who have significant mucosal disease, especially colorectal cancer.

Of the many different brands of faecal occult blood test available, each has a different sensitivity for blood and this will influence its clinical performance. A test that is too sensitive will give too many false positive results and may be of less value than symptoms in identifying patients likely to have mucosal disease, whereas one that is insufficiently sensitive will produce too many false negative results.

It is not known which faecal occult blood test which is most suitable for detecting large bowel disease in symptomatic patients Haemoccult® (Rohm Pharma, Darmstadt, FRG) is the test which has been most widely studied in symptomatic patients with known colorectal disease in order to assess its potential for use in population screening[1,2]. It is relatively insensitive to blood, requiring approximately five times the normal daily blood loss to give a positive result[3,4]. Little is known of its ability to detect non-neoplastic disease. The Fecatwin test (Nordic Pharmaceuticals, USA) is more sensitive for blood than Haemoccult and there is evidence that it can detect inflammatory bowel disease[5]. E-Z Detect® (NMS Pharmaceuticals, USA) is a product that has a different method of use and is effectively less sensitive than Haemoccult.

This study compares three stool tests, with different sensitivities for blood, to determine which is best suited to use in symptomatic patients for the detection of cancer and non-malignant mucosal disease.

Patients and methods

One of three different types of faecal occult blood test was sent at random to every adult out-patient (17 years or over) having a double-contrast barium enema examination in the Southampton and South West Hampshire District during a 15 month period. It was assumed that all these patients had symptoms attributable to the large bowel. Patients were excluded if their appointment was within 7 days of the request being received from a physician as there was insufficient time to complete the faecal occult blood test and the radiograph bowel preparation There was no upper age limit for inclusion in the study Patients received a letter of instruction to complete a 3-day test or, for those with infrequent bowel action, on three consecutive bowel movements, bulking agents or laxatives were not used.

Occult blood tests

Haemoccult is presented as a cardboard pack containing a guaiac-impregnated filter paper with cardboard spatulas for stool sample collection. Two specimens of faeces were collected from different parts of a stool and applied to separate 'windows' in the Haemoccult pack for each day's test. The tests were stored in an envelope supplied and returned by post when all 3 days' tests had been completed Processing was carried out, without rehydration, as soon as the test was received to avoid possible effects of storage and read by a single observer (J.J.T.T.). Any trace of blue coloration in any one or more of the six 'windows' was recorded as a positive result

Fecatwin consists of a guaiac-impregnated filter paper contained within a plastic case with wooden spatulas for collection of faeces. The method of use and processing is the same as for Haemoccult Fecatwin also includes an immunological test for blood which requires special processing; this was not used

The E-Z Detect test contains five filter papers impregnated with benzidine and an oxidizing (processing) agent A paper was placed in the toilet bowl with the stool and if blood was present a colour change occurred. The test was read by the patient and repeated for 3 days. A positive and negative control was included, the former demonstrated to the patient what a positive result would look like and the latter excluded false positive reaction from substances in the water supply. Results were recorded by the patient on a postcard and returned to the hospital

Investigation

Double-contrast barium enema was performed in the usual way in all patients, the examiner being unaware of the faecal occult blood test result Where a junior radiologist performed barium enema a standard

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series of views were taken and the films were reviewed by a consultant or senior registrar. The final diagnosis was that stated in the official radiological report and in those cases where an abnormality was suspected but not proven it was assumed to be present in every case.

Results were compared using the χ^2 test with Yates' correction

Results

A total of 1025 completed tests or result cards were received from patients having barium enema. The age of patients completing the three different tests was similar (*Table 1*). No name was written on 15 tests and 11 tests had not been completed for 3 days; these 26 were excluded from the study. Thirty patients who completed a test correctly either did not attend for their radiography or the examination was unsatisfactory and no radiological diagnosis was made; these patients were excluded also. The radiological diagnosis and correlation with faecal occult blood test results in the remaining 969 patients are shown in *Table 2*.

There was a total of 49 patients (5·1 per cent) with colorectal cancer in the study, 92 patients (9·5 per cent) with a cancer or polyp 5 mm diameter or greater and 130 patients (13·4 per cent) with some mucosal abnormality. Of the polyps, only four were less than 1 cm in diameter and only one of these cases had a positive stool test (Fecatwin). There was no statistically significant difference in the proportion of patients with mucosal diseases in each of the three groups studied.

The difference in sensitivity for cancer of the three tests was not statistically significant. For benign and malignant neoplastic disease combined, Fecatwin was more sensitive than E–Z Detect and this difference was statistically significant ($\chi^2 = 6{\cdot}2$, $P = <0{\cdot}02$). The sensitivity of Haemoccult lay between these two.

When all mucosal abnormalities (cancer, polyps 5 mm or more, inflammatory disease, strictures and other mucosal lesions) are considered together the same trend was seen with 24 of 47 (51 per cent) cases detected by Haemoccult, 29 of 42 (69 per cent) detected by Fecatwin and 11 of 41 (27 per cent) detected by E–Z Detect. Haemoccult was significantly better than E–Z Detect ($\chi^2 = 4{\cdot}44$, $P = <0{\cdot}05$) and the difference between Fecatwin and E–Z Detect was significant also ($\chi^2 = 13{\cdot}2$, $P = <0{\cdot}001$). The difference between Fecatwin and Haemoccult does not reach statistical significance.

Simple statistical analysis of the performance of the three tests for the detection of cancer, neoplasia and all mucosal disease is given in *Tables 3, 4* and *5* respectively. The method of calculation of these values is illustrated in *Table 6*.

Table 1 *Age of patients*

		Age (years)	
	n	Range	Median
Haemoccult	326	19–89	62
Fecatwin	361	29–95	63
E–Z Detect	338	18–86	62

Discussion

The sensitivity of each occult blood test in this study reflects how many cases of a disease have been correctly identified. These values are considered with the specificity which takes account of how many false positive results the test produces. A trend emerges, showing that increasing sensitivity is linked

Table 3 *Detection of cancer by faecal occult blood test*

	Sensitivity	Specificity	Positive predictive value	Overall accuracy
Haemoccult	80·0	88·8	32·7	88·3
Fecatwin	93·3	71·6	13·3	72·5
E–Z Detect	57·1	88·9	19·0	87·5

Values are percentages

Table 4 *Detection of neoplasia* by faecal occult blood test*

	Sensitivity	Specificity	Positive predictive value	Overall accuracy
Haemoccult	62·9	90·4	44·9	87·3
Fecatwin	77·8	72·7	20·0	73·1
E–Z Detect	36·7	89·3	26·2	84·3

Values are percentages * Carcinomas and adenomas

Table 5 *Detection of mucosal abnormality* by faecal occult blood test*

	Sensitivity	Specificity	Positive predictive value	Overall accuracy
Haemoccult	51·1	90·7	49·0	84·9
Fecatwin	69·0	74·1	27·6	73·4
E–Z Detect	26·8	88·8	26·2	80·9

Values are percentages. * Carcinomas, adenomas and inflammatory bowel disease

Table 6 *Table for calculation of simple statistical values*

	Disease present	
	Yes	No
Faecal occult blood test		
Positive	A	B
Negative	C	D
Sensitivity	=A/A+C	
Specificity	=D/D+B	
Positive predictive value	=A/A+B	
Overall accuracy	=A+D/A+B+C+D	

Table 2 *Diagnosis and results of faecal occult blood tests*

	Overall		Mucosal disease					Non-mucosal disease	
	n	Positive (%)	Cancer	Polyp (5 mm or more)	Colitis	Stricture	Other	Diverticular disease	Normal
Haemoccult positive	49 (15·3)		16	6	1	1	–	14	11
Total in group	315		20	15	7	2	3	119	149
Fecatwin positive	105 (31·3)		14	7	6	2	–	34	42
Total in group	335		15	12	7	2	6	114	179
E–Z Detect positive	42 (13·2)		8	3	–	–	–	11	20
Total in group	319		14	16	7	1	3	94	184

with decreasing specificity. The positive predictive value indicates the chance that a patient with a positive test has a given abnormality and, although sensitivity is an important parameter, predictive value may be of more clinical relevance. Statistical calculation of overall accuracy for each test includes not only those who had disease and a positive test, but also those who had no mucosal abnormality in whom the faecal occult blood test was negative. There was a large number of patients in the study with no mucosal abnormality and a negative stool test. High values of 'accuracy' were found which should be interpreted with caution

Haemoccult does not detect all cases of colorectal cancer but gives few false positive results and it is this combination that has proved to be the best compromise for population screening. This study shows that it can detect a little over half of all mucosal disease demonstrable on double-contrast barium enema. The predictive value of a positive Haemoccult test for all abnormalities was 49 per cent and most of these will be cases of cancer. This predictive value is likely to be considerably greater than that which could be achieved clinically. Rectal bleeding is the most significant symptom but has a predictive value for colorectal cancer of only 8–17 per cent[6–8]. Haemoccult might be particularly suitable, therefore, for the selection of patients, without obvious disease, for urgent investigation. While this would be of use in the hospital environment it may be of greater benefit in the community. If the test were performed by general practitioners it might reduce diagnostic delay which affects up to two-thirds of patients with serious colorectal disease[9]. Haemoccult could identify, among patients with common large bowel symptoms, those requiring immediate specialist investigation or referral. The converse does not apply, however, and a negative Haemoccult test does not exclude serious pathology. Such a result should be disregarded and must not influence patient management.

Fecatwin, being more sensitive for blood than Haemoccult, has been shown to have a higher sensitivity for cancer – equal to that achieved by double-contrast barium enema itself[10,11] – and to detect more than two-thirds of all mucosal diseases. It appears to have an advantage over Haemoccult not only for cancer detection but particularly for inflammatory bowel disease. Its positive predictive value is relatively low because there are many false positives (a patient with a positive Fecatwin test has just over 1:8 chance of having a colorectal cancer whereas for Haemoccult the figure is 1:3) Fecatwin may be of only limited additional help to routine clinical consultation and examination in identifying symptomatic patients with cancer or other significant mucosal diseases. On the other hand, Fecatwin is so sensitive that there may be some cases in which the stool test is correct and the radiograph is false negative. Colonoscopy might show some abnormality in these patients. Double-contrast barium enema has been reported to miss 5–16 per cent of colorectal cancers[12,13] and this figure is almost certainly higher for inflammatory bowel disease. If Fecatwin identifies mucosal disease which radiography misses it could be of use as a simple quality control check for double-contrast barium enema – for example by identifying patients whose films should be double viewed[10]. On the basis of the results achieved in this study, colonoscopy cannot be recommended automatically for Fecatwin-positive patients as the test lacks specificity.

Given the results for Haemoccult, it is not surprising that a test which is effectively less sensitive for blood gives a disappointing performance. E–Z Detect failed to identify almost half the cases of colorectal cancer without any reduction in the number of false positive results to offset this disadvantage. Unfortunately all faecal occult blood tests are prone to false positive reactions with substances in the stool other than blood, particularly vegetable peroxidases[14]. E–Z Detect may be especially prone to false positive reactions as a consequence of the different method of use of E–Z Detect compared with the other two tests In symptomatic patients, the sensitivity of Haemoccult for blood may be as low as is practical.

Some patients were excluded from the study because their appointments did not allow time to complete a test; however, this group amounted to only 6 per cent of the total number entered. For the same reason, inpatients were not studied. A surprising number of cancers are only diagnosed when the patient is admitted to hospital. It is felt that this explains why the number of cancers in the study was lower than expected and why the difference in the tests' ability to detect cancer did not reach statistical significance. Significant differences were demonstrated for the detection of all mucosal abnormalities combined and it is likely that similar differences do exist for cancer detection

A recent report[15] of the use of Fecatwin employing both the guaiac and immunological components demonstrated good results. If the high sensitivity of the test could be combined with a predictive value similar to that achieved by Haemoccult, then Fecatwin would be a very powerful diagnostic aid in symptomatic patients.

In conclusion, this study shows that a patient with symptoms of large bowel disease and a positive Haemoccult test has a 50 per cent chance of mucosal disease, especially cancer, and should be investigated. If double-contrast barium enema is negative subsequent colonoscopy may be indicated. A negative Haemoccult test should not influence the management of symptomatic patients because treatable disease will be missed if investigations are withheld on this basis. A faecal occult blood test less sensitive for blood than Haemoccult is unlikely to be of clinical value in symptomatic patients. The more sensitive Fecatwin test identified 69 per cent of those with mucosal disease detectable on double-contrast barium enema. Measured performance might have been better had all patients been investigated by colonoscopy but there were three times as many false positive reactions, which adds to the burden of screening with this test. Fecatwin probably has the maximum sensitivity for blood that is of value in identifying colorectal disease

Acknowledgements

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New technique for temporary purse string suture in stapler anastomosis

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The procedure of stapler anastomosis in oesophageal, intestinal and colorectal surgery requires the placement of temporary purse string sutures. These sutures are used to draw the cut edges of both intestinal segments around the stapling device before closure of the instrument[1–3]. A new technique is presented.

Technique

The principle of the automatic instrument (Purstring®, US Surgical Corporation, Norwalk, Connecticut, USA) is the placement of a circumferential suture held in place by stainless steel staples. The disposable instrument consists of a forceps with two ring handles and a safety handle lock. Two jaws, 70 mm in width, each contain 14 staples of 0·2 mm diameter stainless steel wire arranged in a single row 58·4 mm long. In a slot the jaws carry a strand of 2/0 monofilament nylon.

The jaws are opened by spreading the ring handles and are placed across the structure where a temporary purse string closure is required. The ring handles are closed until the safety catch engages (*Figure 1*). When exact placement on the tissue is established, the safety catch is released and the instrument is activated by squeezing the ring handles until they lock together. Before removal the instrument edge is used as a cutting guide to transect the tissue (*Figure 1*). This will ensure cutting at a proper distance from the purse string. After releasing the instrument, the nylon purse string can be completely drawn out from the slot of the jaws (*Figure 1* inset). The stapling device is then inserted into the intestinal lumen and the purse string suture is closed around the instrument. The steel staples fixing the purse string suture are removed together with the intestinal tissue rings after firing and removal of the stapler.

Discussion

Stapling techniques are being used more frequently, especially for oesophagointestinal and colorectal anastomoses[1]. The purse string sutures which have to be placed before the anastomosis are either inserted by hand as a border suture or by applying a wavelike forceps[2,3]. It is of utmost importance to achieve a regular and safe purse string closure, because incomplete adaptation of the tissue around the stapling device may lead to primary leakage after firing the instrument

The new purse string instrument is easy to handle and leads to a very regular purse string suture. In 21 cases of oesophagointestinal and colorectal anastomoses complete purse string closures around the stapler could be achieved and no leakages of the anastomoses were recorded. The placement of temporary purse string sutures using the new instrument represents a simple, time-saving and safe procedure However, for application at the mediastinal oesophagus through the diaphragm or at the rectum low in the pelvis, the new device is often too large and smaller instruments with jaws of 40–50 mm are necessary.

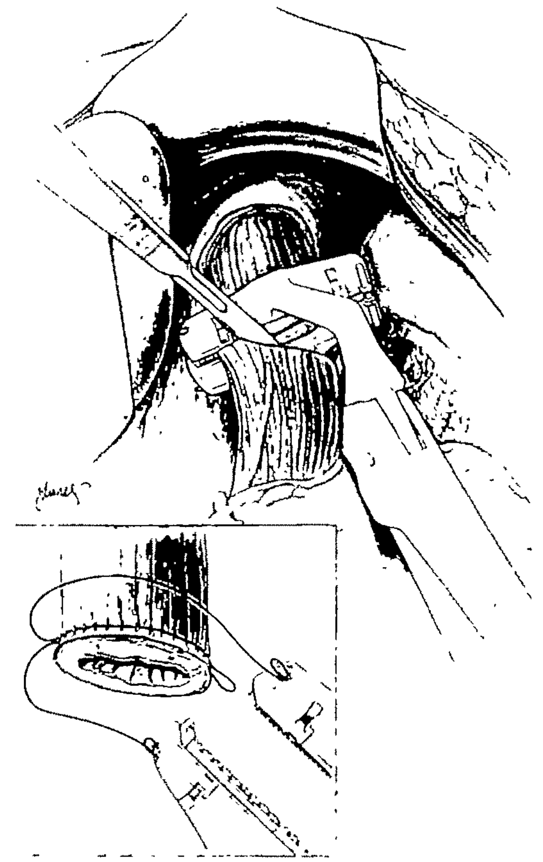

Figure 1 *Application of the purse string instrument at the oesophagus in total gastrectomy. The oesophagus is cut at the instrument edge Inset: after removal of the instrument the circumferential suture is attached to the oesophageal edge by small stainless steel staples*

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Whole gut irrigation and Prepacol® laxative preparation for colonoscopy: a comparison

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Two techniques for preparation of the colon for colonoscopy were compared in a controlled trial. Fifty patients given a low residue diet and the laxative Prepacol® were compared with 50 patients given whole gut irrigation. Significantly more patients suffered from vomiting ($P=0.0005$), *shivering* ($P=0.0062$) *and nausea* ($P=0.031$) *following irrigation; in two cases the procedure had to be abandoned because of profuse vomiting. Irrigation was less well tolerated by the patients* ($P=0.00002$) *than preparation with Prepacol®. On the other hand, the quality of bowel preparation was found to be better* ($P=0.0005$) *after irrigation. On two occasions colonoscopy was not possible following Prepacol® preparation because of faecal residue. Patients with a previous colorectal resection showed a similar quality of cleansing to those patients prepared with irrigation. We conclude that Prepacol® is as efficient as irrigation for patients who have had a previous colorectal resection because the quality of bowel preparation is as good and the associated patient discomfort is small.*

Keywords: Whole gut irrigation, Hewitt's solution, Prepacol®, colonoscopy

Adequate colon preparation before diagnostic and therapeutic procedures is important because safety and diagnostic accuracy depend on adequate visualization[1]. Cleansing can be achieved with laxatives, enemas[2,3], whole gut lavage with Hewitt's[4] or Golytely® solution[5,6], and dietary measures[7] used either alone or in combination.

Standard techniques such as laxatives, dietary measures and cleansing enemas are time consuming, uncomfortable for the patient and frequently unsatisfactory[8]. As an alternative, rapid enteral administration of saline or balanced salt solutions have been recommended to improve efficiency and patient acceptance for colon preparation before colonoscopy[5,9,10].

We have conducted a randomized trial comparing whole gut irrigation using Hewitt's solution with a technique using the laxative Prepacol® (Nicholas GmbH, Sulzback, FRG), a combination of sodium hydrogen phosphate and bisacodyl.

Patients and methods

The study included 100 consecutive patients undergoing elective colonoscopy over a 5-month period. Criteria for exclusion included heart or kidney insufficiency, pregnancy, partial colonic obstruction and emergency colonoscopy. After patients had provided informed consent, a careful history was documented and a physical examination was performed.

A computer-generated randomization was used to assign patients to either group A (irrigation with Hewitt's solution) or group B (preparation with Prepacol®).

Group A

These patients were not subjected to any dietary restrictions until the day of preparation, which was the day of colonoscopy. Baseline body-weight, heart rate and blood pressure values were measured. Sodium, potassium, leucocyte count, haemoglobin and haematocrit were measured in the peripheral venous blood. An arterial blood gas analysis was performed. These measurements were repeated 1 h after irrigation (*Figure 1*).

A nasogastric tube (16 Charrière) was then inserted and prewarmed Hewitt's solution was infused at a rate of 2–3 l/h until stool outflow was clear or a total of 10 litres had been given.

Group B

Three days before colonoscopy the above clinical and blood parameters were measured. Colon preparation was started on the following day. Dietary restriction forbade bread, vegetables, fruit juice, carbonated water and milk. A minimum of 2 litres fluid per day was required. On the day before colonoscopy a solution of 30 ml sodium monohydrogen phosphate and sodium dihydrogen phosphate, and 2 h later 20 mg bisacodyl were taken (*Figure 1*).

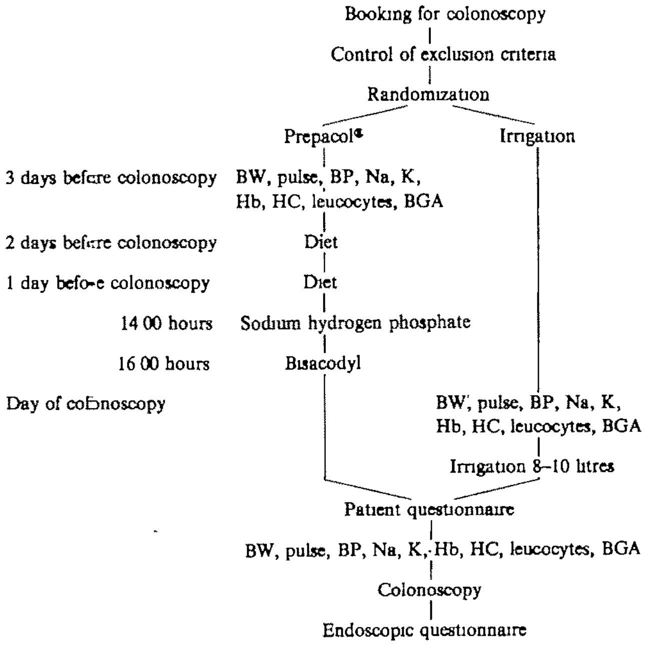
Booking for colonoscopy
Control of exclusion criteria
Randomization
Prepacol®
Irrigation
3 days before colonoscopy
BW, pulse, BP, Na, K, Hb, HC, leucocytes, BGA
2 days before colonoscopy
Diet
1 day before colonoscopy
Diet
14 00 hours
Sodium hydrogen phosphate
16 00 hours
Bisacodyl
Day of colonoscopy
BW, pulse, BP, Na, K, Hb, HC, leucocytes, BGA
Irrigation 8–10 litres
Patient questionnaire
BW, pulse, BP, Na, K, Hb, HC, leucocytes, BGA
Colonoscopy
Endoscopic questionnaire

Figure 1 *Study design. BW, body-weight; BP, blood pressure; Na, sodium; K, potassium; Hb, haemoglobin; HC, haematocrit; BGA, blood gas analysis*

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Conduct of the study

Before entering the endoscopy room, patients were asked to assess the comfort/discomfort of the colon preparation according to a questionnaire. Flatulence, abdominal and anal pain, nausea, vomiting, headache, vertigo, shivering and tiredness were documented and the severity was assessed as either considerable, moderate or absent. Patients were also asked whether the preparation was very bothersome, onerous, slightly onerous or not onerous at all, and whether they would agree to undergo this preparative procedure again

Two experienced colonoscopists, blinded as to the type of preparation used, scored the quality of preparation according to the following grading system,

(a) *Excellent* no faecal residue present;
(b) *Good* minimal faecal material, not interfering with interpretation of the colonoscopy;
(c) *Fair* moderate faecal debris, small polyps up to 5 mm could not be excluded;
(d) *Poor.* marked faecal residue, inability to interpret the colonoscopic results.

The quality of preparation for each colonic segment examined (caecum and ascending, transverse, descending and rectosigmoid colon) was documented.

Statistics

Paired data were analysed using Fisher's exact test, unpaired data using Student's *t* test ($P \leqslant 0{\cdot}05$ was considered to be significant). Correlations between metric and non-metric data were assessed by using the Spearman correlation coefficient (significant for $|t|>2$).

Results

Characteristics of the study population

Group A and B patients were similar in age, sex, status (ambulatory or hospitalized colonoscopy), indication for colonoscopy and previous gastrointestinal operations (*Table 1*).

The irrigation had to be stopped in two group A patients because of profuse vomiting. Thus, only 48 group A patients were actually colonoscoped.

Forty-eight patients in group B followed their diet accurately and all 50 patients completed the preparation. One patient took the laxative 1 day too early and colonoscopy had to be interrupted due to the presence of too much faecal residue.

Endoscopic findings and quality of preparation

The endoscopic findings and interventions performed are listed in *Table 2*. The time that elapsed before reaching the ileum was similar, although two patients prepared with Prepacol® had so much stool in the colon that colonoscopy was not possible.

Table 1 *Patient characteristics*

	Group A irrigation	Group B: Prepacol®
n	50	50
Age (years)	60·3 (13 9; 17–85)	55·3 (17 6, 22–80)
Sex (male:female)	17:13	21.29
Interruption of preparation	2	–
Ambulatory:hospitalized	10·40	14:36
Indication for colonoscopy		
Tumour search	23	29
Abdominal pain	16	12
Colon follow-up	11	9
Previous gastrointestinal operations		
Right hemicolectomy	3	2
Left hemicolectomy	2	1
Sigmoid resection	–	2
Low anterior resection	1	6
Abdominoperineal resection	2	–
Colon segment resection	–	2
Appendicectomy	12	8
Other (stomach), small bowel)	7	5

Values in parentheses are s d. and range

Table 2 *Endoscopic findings, reasons for interruption of colonoscopy, endoscopic interventions and time elapsed in reaching the ileum*

	Group A irrigation (*n*=48)	Group B· Prepacol® (*n*=50)
Time to ileum (min)	16·2 (9·5; 5–40)	14·3 (7 8; 4–40)
Duration of colonoscopy (min)	24·4 (14·3; 7–60)	20·4 (10·4; 5–45)
Interruption of colonoscopy		
None	42	43
Obstructing tumour	4	2
Poor preparation	–	2
Pain	2	3
Endoscopic findings		
Normal	17	22
Diverticulosis	11	10
Diverticulitis	2	–
Adenoma	1	3
Carcinoma	4	5
Polyps	15	9
Other	3	3
Endoscopic intervention		
None	32	38
Biopsy	5	7
Polypectomy	11	6

Values in parentheses are s d. and range

Table 3 *Quality of preparation*

	Group A: irrigation (*n*=48)		Group B: Prepacol® (*n*=50)		*P*
Excellent	29	47	8	37	0 0005
Good	18		29		
Fair	1	1	11	13	
Poor	–		2		

There were no differences in the distribution of endoscopic findings between the two groups. In the Prepacol® group, fewer polyps were visualized, but this difference was not significant ($P=0{\cdot}098$). The analysis of colon cleansing score showed a significantly better preparation following whole gut irrigation ($P=0{\cdot}0005$) (*Table 3*). The localization of residual faeces after preparation showed that Prepacol® does not clean the caecum and ascending colon as efficiently as irrigation, while cleansing of the transverse, descending and rectosigmoid colon was nearly equal in both groups. The quality of preparation after Prepacol® was equal to that of irrigation in patients with a previous colorectal resection.

Weight, vital signs and biochemical measurements

Comparison of all measurements showed no difference between the two groups before preparation. After irrigation, potassium, haemoglobin and haematocrit decreased significantly; sodium, sodium bicarbonate, pH, base excess, systolic blood pressure and body-weight increased significantly. Preparation with Prepacol® led to a significant decrease in potassium, haematocrit, P_{O_2} and body-weight.

These changes in biochemical and clinical measurements did not require any therapeutic intervention

Patient comfort

During irrigation, vomiting ($P=0{\cdot}0005$), shivering ($P=0{\cdot}0062$) and nausea ($P=0{\cdot}031$) were significantly more common than

Table 4 *Patient reaction to the preparation for colonoscopy*

	Group A: irrigation ($n=50$)		Group B: Prepacol® ($n=50$)		*P*
Very bothersome	13	27	2	7	0·00002
Onerous	14		5		
Slightly onerous	15	23	16	43	
Not a problem	8		27		

during preparation with Prepacol®. Of the 50 patients in group B, 49 stated they would agree to use this form of preparation again, while 20 of the 50 patients in group A stated they would refuse irrigation again. Twenty patients in the Prepacol® group have previously been prepared by irrigation, and 19 of these stated that they would prefer to take Prepacol®.

The comfort/discomfort score showed that whole gut irrigation is significantly less well tolerated than the use of Prepacol® ($P=0{\cdot}00002$) (*Table 4*).

Discussion

Adequate colon cleansing for diagnostic and therapeutic procedures is extremely important. Furthermore, follow-up after operation or endoscopic polypectomy is acceptable to the patient only if the preparation and the colonoscopy are not too painful or bothersome. End-points of a trial studying colon cleansing techniques must include the adequacy of colonic visualization, side-effects related to the method, and patient comfort.

Conventional colon cleansing methods (1–3 days of clear liquids, laxatives and enemas) provide a relatively faeces-free colon but are time consuming, inconvenient and uncomfortable for the patient[3]. In order to improve preparation, whole gut lavage solutions were developed. In this study irrigation was found to be significantly better than Prepacol® when the quality of cleansing was considered Other randomized trials comparing conventional 2 or 3-day bowel preparation with whole gut lavage have shown that the quality of cleansing after irrigation is superior[3,11,12]. On the other hand, our study has shown that the quality of cleansing with Prepacol® was similar to irrigation when patients had had a previous colorectal resection.

Another important aspect of colonic preparation for colonoscopy is the associated metabolic changes[5,13,14]. We found significant changes in metabolic factors after both whole gut irrigation with Hewitt's solution and Prepacol®. In healthy patients these changes are negligible; however, they may be of importance in patients with heart or kidney disease.

Patient acceptance of follow-up after colorectal operation or endoscopic polypectomy depends in part on the amount of discomfort associated with the endoscopic procedures and bowel preparation Some authors have stated that conventional colon cleansing methods are uncomfortable for the patient while whole gut irrigation may be more comfortable[3]. However, in a survey carried out by Downing *et al.*[15] 17 per cent of patients developed abdominal pain and 30 per cent experienced nausea and vomiting during irrigation. We were able to confirm these findings: 10 per cent of our patients experienced abdominal pain, 10 per cent had anal pain, 26 per cent had vomiting, and 14 per cent had shivering during irrigation. In contrast, patients prepared with Prepacol® reported a significantly lower rate of nausea, vomiting and shivering. Furthermore, patients prepared with irrigation stated significantly more often that the preparation was either very bothersome or onerous Forty per cent of patients did not want to undergo a repeat preparation with irrigation. These results are similar to those of Downing *et al.*[15]: 29 per cent of patients stated they would refuse irrigation for a subsequent preparation.

In the UK, Picolax® (Nordic Pharmaceuticals Ltd., Feltham, UK), which like Prepacol® is an osmotic cathartic agent, is widely used. De Lacey *et al.*[16] showed that the colon was as well prepared by Picolax® without washout as it was by colonic lavage. Roe *et al.*[17] showed that Picolax® produced a cleaner bowel than that achieved by enema and washout preparation. Unfortunately there are no randomized trials comparing Prepacol® and Picolax®.

In summary, Prepacol® is recommended for patients who have had a colorectal resection because patient comfort is better and the quality of cleansing is as good as with irrigation Prepacol® also provides satisfactory preparation in patients who have not had previous colorectal operations.

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Percutaneous transhepatic cholangioscopic lithotripsy

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Since 1983, 14 patients with intrahepatic and common bile duct stones have undergone percutaneous transhepatic cholangioscopic lithotripsy because the stones were too large to be removed using ordinary percutaneous transhepatic cholangioscopy. Stones were completely fragmented in seven cases (six with intrahepatic stones and one with common bile duct stone) and partially disrupted in five cases with intrahepatic stones. Intrahepatic duct angulation and stricture was the factor most often responsible for failure. All the disintegrated stones were removed by subsequent transhepatic cholangioscopy. Amongst the seven patients with complete stone fragmentation, six stones were found with electrohydraulic shock-wave lithotripsy and one with NdYAG laser lithotripsy. Complications of percutaneous transhepatic cholangioscopic lithotripsy using electrohydraulic shock waves were found in three cases, two had transient haemobilia and one had fever and chills after the procedures. They all recovered by conservative treatment. NdYAG laser treatment was expensive, time consuming and inconvenient to use. Percutaneous transhepatic cholangioscopic lithotripsy by using electrohydraulic shock wave is an effective and safe method to fragment biliary stones and to facilitate their removal.

Keywords: Percutaneous transhepatic cholangioscopic lithotripsy

Percutaneous transhepatic biliary drainage can be life saving in biliary sepsis and has been proposed as an alternative to surgical decompression[1–4]. Percutaneous transhepatic cholangioscopy is an effective and safe method for the management of biliary stones; the success rate of stone removal from common bile duct and intrahepatic ducts is approximately 80 per cent[5–7]. Large stones, however, continue to present a therapeutic problem. Current strategies include chemical dissolution[8,9], and disintegration of stones using mechanical fragmentation[10,11], lasers[12], ultrasonic probes[13] and electrohydraulic shock waves[14]. The purpose of this paper is to review our experiences with 14 patients who underwent percutaneous transhepatic cholangioscopic lithotripsy for biliary stones by using a mechanical lithotriptor, a NdYAG laser and electrohydraulic shock waves.

Patients and methods

Patients

Over the period June 1983 to June 1988 at the Chang Gung Memorial Hospital, Taipei, percutaneous transhepatic cholangioscopy was performed on 50 patients with stones in the intrahepatic ducts or common bile duct. Successful stone removal was achieved in 32 cases, seven of whom had common bile duct stones and 25 intrahepatic duct stones. Failure of stone removal in the majority was attributable to the presence of large, impacted stones and biliary strictures. Over the same period, 14 patients underwent percutaneous transhepatic cholangioscopic lithotripsy to fragment large or impacted stones and facilitate their removal. There were 2 men and 12 women, aged 26–78 years. Percutaneous transhepatic catheterization and drainage was carried out because of biliary colic, obstructive jaundice and cholangitis. Among the 14 patients, seven had a previous history of repeated biliary tract operations and were unwilling to have further surgery. Two were considered to be high risk patients because of advanced age and five were treated in the presence of septic shock. A mechanical lithotriptor (stone crush forceps and hand-drill), a laser and electrohydraulic shock wave lithotripsy were used to fragment stones under direct vision during cholangioscopy.

Technique

The standard percutaneous transhepatic biliary drainage was performed in the usual manner through right ducts or left ducts. The fistula tract was dilated at intervals of 1 week until a suitably sized tract (18–20 Fr) was formed. The choledochoscope was inserted through the fistula orifice. Grasping forceps could be inserted through the instrument's channel to remove stones[5,6]. Stone crushing forceps, the probe of the electrohydraulic (EHL) shock wave lithotriptor and a laser catheter could also be introduced into the bile ducts via the same channel to perform lithotripsy. Cholangioscopy and lithotripsy could both be performed in the out-patient clinic. Most of the patients could tolerate cholangioscopy and/or lithotripsy without medication. When necessary, 50 mg pethidine was given intramuscularly. Ampicillin (500 mg orally every 6 h) was prescribed for 3 days.

Instruments

An improved fibreoptic choledochoscope (CHF 4B, Olympus Optical Co., Tokyo) was used. This instrument has a flexible distal tip, 5 mm in diameter, and can bend 160° upwards and 90° downwards. It is also equipped with a forceps channel, allowing passage of stone crushing forceps, lithotriptor probes and laser fibre.

The laser beam (NdYAG laser, model 621, MBB Inc., Munich, FRG) was inducted into a quartz fibre surrounding a 0.6 mm diameter Teflon® (E. I. du Pont de Nemours and Company, Wilmington, Delaware, USA) tube.

An electric surge current generator (electrohydraulic lithotriptor, Model EC-27080, Karl Storz GmbH, Tuttlingen, FRG) was used to produce high-voltage electric sparks of 5 μs duration between two coaxial electrodes at the tip of the lithotriptor probe in the presence of normal saline solution.

Results

Effectiveness

Altogether 51 sessions of lithotripsy were performed on the 14 patients with biliary stones. Left ducts were entered in 10 patients, and right ducts in four. Biliary stones were successfully fragmented in six of 12 patients with intrahepatic stones and one of two patients with common bile duct stones. Stones were partially crushed in five patients with intrahepatic duct stones (*Table 1*). All the disintegrated stones were removed at subsequent cholangioscopy. Removal of all stones was checked on completion of endoscopy, and in some cases by cholangiography performed through the fistula tract.

In the group of patients undergoing EHL shock-wave lithotripsy, the method failed to crush any stones in two cases

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Table 1 *Results of percutaneous transhepatic cholangioscopic lithotripsy (PTCS-L) in 14 patients with biliary stones*

	No. of patients	No. of sessions PTCS-L	Stone fragmentation	
			Partial	Complete
Mechanical lithotriptor (stone crush forceps, hand drill)	6*	12	2	0
NdYAG laser	2	4		
Electrohydraulic shock wave	10	35	2	6

* Four of six also underwent electrohydraulic shock-wave lithotripsy

Table 2 *Comparison between percutaneous transhepatic cholangioscopic NdYAG laser and electrohydraulic shock-wave lithotripsy in treatment of biliary stones*

	NdYAG laser	Electrohydraulic shock wave
No. of patients	2	10
No. of shots	30–200	2–40
Duration of treatment (min)	60–120	20–60
Maximum diameter of stones (mm × mm)	15 × 15	20 × 15
Failure of treatment	Sharply angled and tortuous duct	Sharply angled and tortious duct
Haemobilia	1	2
Subjective symptoms	Burning sensation	Pain
Preparation of equipment	Complicated, needs experienced assistant	Convenient, less time consuming

because the stones were lodged in tortuous or angular intrahepatic ducts, so that the tip of the lithotripsy probe could not reach the stone surface. Repetition of lithotripsy was required in most cases, the average number of performances per patient being 3·3 (range 1–8). *Table 2* summarizes the results of NdYAG laser and EHL shock-wave lithotripsy.

Complications

There was no mortality in either group treated with laser and shock-wave lithotripsy. Complications were few. Three patients were found with haemobilia following the use of EHL shock waves and the YAG laser (*Table 2*). A stent tube was inserted into the percutaneous transhepatic tract, and irrigation with normal saline solution was performed. Haemobilia disappeared 1 day later without further complication[5]. One patient developed fever and chills after lithotripsy. He responded to nasogastric suction, intravenous administration of fluid and antibiotics.

Discussion

Intrahepatic stones are common in South-East Asia and remain a difficult problem to manage[15–19]. Retention of stones in the intrahepatic ducts and common bile duct is a frequent and troublesome complication, which in many cases necessitates repeated operation because of recurrent cholangitis[18,19]. With recent improvements in fibreoptic choledochoscopes and the development of percutaneous transhepatic catheterization techniques, choledochoscopy has allowed non-surgical removal of biliary stones[15–17]. However, basket forceps manipulation is often difficult, or even impossible, especially in patients with huge or impacted stones in the intrahepatic ducts. Stricture of hepatic ducts also makes advancement of the basket forceps impossible[15–17].

Electrohydraulic lithotripsy allows stones to be crushed by means of shock waves generated by an electric discharge in a liquid medium[14]. It has been applied under fluoroscopic guidance or during choledochoscopy through a T tube tract[20] or percutaneous transhepatic tract[21,22], or by duodenoscopy after sphincterotomy[21,23]. It has been shown to be an effective method of fragmenting biliary stones. Ductal perforation and mucosal damage causing haemorrhage are the most frequent complications[14,21–23]. To prevent this, avoidance of contact of the electrodes of the lithotriptor probe with the stone is recommended. The electrohydraulic shock wave can theoretically disintegrate a stone without direct contact of the probe with the stone. With the use of direct vision by choledochoscopy, the probe is kept in close proximity with the stone during application of the discharge sparks and so avoids any damage to the bile duct wall.

A NdYAG laser has been used to treat alimentary tract disease, especially gastrointestinal bleeding. Orii *et al.* first successfully applied the NdYAG laser using choledochoscopy via a T tube tract to disrupt biliary stones[12]. However, percutaneous transhepatic laser therapy has not been widely accepted in clinical use because it is expensive and inconvenient[12]. Also, it only disrupts bilirubin stones in a liquid medium; breaking cholesterol stones is almost impossible. During NdYAG laser lithotripsy, the catheter should be applied directly to the stone because it will damage the tissue when the beam radiates in other directions[12]. Because of these considerations, percutaneous transhepatic cholangioscopic lithotripsy using electrohydraulic shock waves appears by far the most effective and safe method of fragmenting biliary stones and facilitating their removal.

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Case report

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Subcutaneous fat necrosis in pancreatic disease

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Erythema nodosum-like lesions of fat necrosis in cases of pancreatitis and pancreatic carcinoma are rare. Such lesions were first described in 1883 by Chiari, and since that time some 40 case reports have appeared, although only three cases are recorded in the UK literature[1–3]. We have seen three patients in the past 20 years in whom an initial diagnosis of erythema nodosum was suggested. Skin biopsy led to recognition of major pancreatic disease in two cases.

Case report

Case 1

A 53-year-old heavy drinker was admitted with acute pancreatitis and treated conservatively. His recovery was complicated only by transient arthritis of the right first metatarsophalangeal joint, clinically thought to be gout, but there was no hyperuricaemia. He was discharged 3 weeks after presentation, but 2 weeks later he developed a crop of tender red nodules on both anterior and posterior aspects of his lower legs, initially diagnosed as erythema nodosum. These nodules persisted, new lesions appearing, and he was referred for a dermatological opinion. A tentative diagnosis of necrotizing panniculitis with pancreatitis was made and confirmed on skin biopsy (*Figure 1*). Other investigations revealed an ESR of 108 mm/h, a white cell count of $15\cdot1 \times 10^9$/l (no eosinophilia), a serum amylase level of 8240 units/l (normal 70–300 units/l) and a serum lipase level of 12·1 Tietz units/l (normal < 7 units/l).

The cutaneous lesions settled over 12 months and did not recur during a subsequent attack of pancreatitis.

Case 2

A 43-year-old housewife was admitted with a 6-month history of weight loss and diarrhoea. Two months before admission she had an attack of pleuritic pain and began developing tender red nodules on the knees and lower legs. The chest pain had cleared with antibiotic therapy but the nodules persisted with new lesions appearing on the buttocks and abdominal wall. Pertinent physical findings included dehydration, cachexia, hepatomegaly and bluish-red, well circumscribed, tender nodules on the shins, dorsa of the feet and the calves. Some nodules had healed leaving depressed, lightly pigmented scars, while others had slightly softened centres.

A differential diagnosis of erythema nodosum or allergic vasculitis was made and a skin biopsy was performed. Histology showed well demarcated areas of subcutaneous fat necrosis and extensive areas of basophilic ghost cell formation, typical of pancreatic disease. Serum amylase concentration was not measured.

The patient continued to lose weight but had no abdominal pain. Ten days after admission she developed pneumonia complicated by uraemia and died. Autopsy revealed considerable ascites. The head and body of the pancreas were almost completely replaced by carcinoma, and the liver and peritoneal surfaces were studded with secondary deposits.

Case 3

A 20-year-old woman with a 10-year history of end stage renal failure secondary to pyelonephritis and vesicoureteric reflux had received a cadaveric renal transport in 1983 at the age of 15 years. In July 1988 her renal transplant began to fail and she started on chronic ambulatory peritoneal dialysis (CAPD). Five days later she developed painful, red, indurated ovoid nodules on both lower legs (*Figure 2*). Similar lesions on the posterior chest wall were fluctuant.

Skin biopsy showed acute panniculitis with necrosis suggestive of pancreatic disease. There was no evidence of vasculitis. Her serum amylase level was found to be raised at 2288 units/l. Three weeks later she began to complain of left upper quadrant pain and increased bowel frequency with stools that were pale, offensive and difficult to flush. Abdominal ultrasound examination showed no abnormality; computed tomographic scan showed a bulky pancreas but no evidence of gallstones, pancreatic abscess or pseudocyst.

The panniculitis resolved over 4 weeks and did not recur, although the pancreatitis persisted with intermittent epigastric discomfort and tenderness. The low amylase level in the peritoneal dialysis fluid (13 units/l) excluded macroamylasaemia, and the pancreatitis was thought to be secondary to her CAPD and high requirement for hypertonic exchange perpetuating pancreatic inflammation. She was therefore changed onto haemodialysis in November 1988 with slow amelioration. However, although now asymptomatic, her serum amylase remains elevated at 713 units/litre.

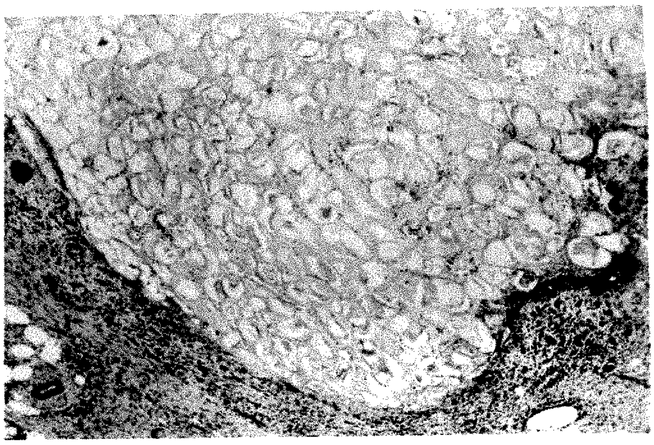

Figure 1 *Histology of a nodule from case 1 showing 'ghost cells' (haematoxylin and eosin stain, × 20). The ghost cells are remnants of fat cells, the contents of which are replaced by calcium soap formation. There is no vasculitis*

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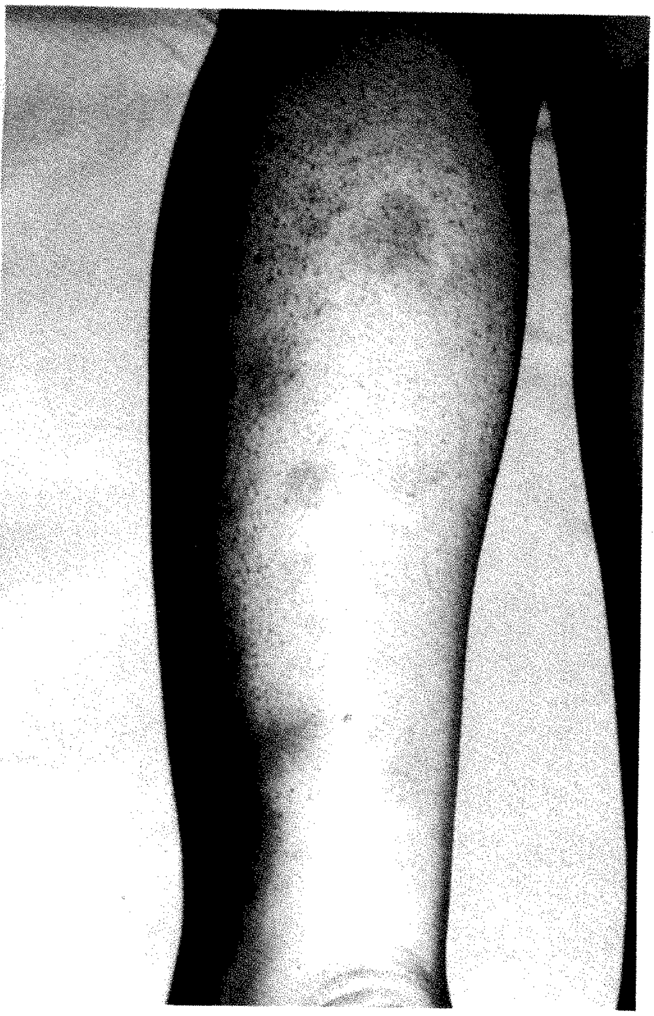

Figure 2 *Red indurated nodules on lower legs (case 3)*

Discussion

The appearance of areas of fat necrosis in the peripheral skin and in and around single joints can accompany pancreatic disease of inflammatory[4], malignant[4] or traumatic[2] origin. The first report of such an association in the UK literature was by Blauvert[3] in 1946. Subsequently Hughes *et al.*[5] reviewed the literature of 53 cases, 36 associated with pancreatitis and 17 with carcinoma. There was a preponderance of males in both groups, but pancreatitis tended to occur in a younger population with a high (47 per cent) incidence of alcoholism. Carcinoma of the pancreas was more often associated with eosinophilia.

The joint lesions are clinically identical to gout but the serum uric acid is not elevated. The cutaneous lesions may be tender and initially mistaken for erythema nodosum. However, although both conditions share a predeliction for the lower legs, lesions in pancreatic disease tend to be more diffuse[4] (e.g. occurring on buttocks, thighs and arms). The skin lesions are of a dull bluish-red appearance with a tendency to central softening. Healing occurs with some scarring and hyperpigmentation, but there is no evidence of 'bruising' or fading as seen in true erythema nodosum.

The skin histology is characteristic showing replacement of fat lobules by calcium soaps and ghost cells[6]. Such a histological picture is not seen in erythema nodosum, allergic vasculitis or Weber–Christian disease and should immediately suggest pancreatic disease.

It is essential that the significance of the cutaneous signs is recognized as they are frequently the patient's presenting complaint[4,7], pancreatic disease remaining asymptomatic[5] (as in case 3). Potts *et al.*[8] expanded the syndrome of cutaneous nodules associated with pancreatic disease to include polyserositis. This has important prognostic implications as in their series of 20 patients with the syndrome associated with pancreatitis, none of the patients with pancreatitis and subcutaneous nodules alone died. However 13 of the 17 patients with associated arthritis, six of seven with concurrent pleural effusion and all five patients with both pleural effusion and arthritis died.

The pathogenesis of the lesions is poorly understood, but it is postulated that subcutaneous fat necrosis occurs secondary to liberation of pancreatic enzymes into the circulation or lymphatics[9], and lipase[10] or amylase[11] have variously been favoured as the principal active agent. It is possible to reproduce fat necrosis experimentally in rats by injection of pancreatic extract into the peritoneal omentum[11]. However other factors may be implicated as neither incubation of human breast tissue with commercial amylase nor incubation of normal human skin with serum from an affected patient can induce fat necrosis[12].

The rarity of the syndrome, in contrast to the frequency of pancreatitis, has prompted the suggestion that an enzyme deficiency may have a possible role in the pathogenesis of lesions[13]. A further paradox is that the serum concentration of pancreatic enzymes may remain raised long after resolution of the cutaneous signs[14] (as demonstrated by case 3), and the syndrome may not recur in subsequent attacks of pancreatitis (illustrated by case 1), implying that elevated levels of pancreatic enzymes in peripheral blood alone are not enough to cause the syndrome. Immune-mediated injury has been considered contributory[8], but the underlying pathogenesis remains obscure. It would, however, appear to be multifactorial in origin.

Recognition of this unusual syndrome with its characteristic histopathology warrants attention as it may be the first clinical indication of serious pancreatic disease.

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Bile duct size after cholecystectomy: an endoscopic retrograde cholangiopancreatographic study

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Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 43 patients before and 4–14 months after cholecystectomy. All patients had a normal common bile duct and were asymptomatic after the operation. Preoperative and postoperative films of adequate quality were available for scrutiny in 35 patients. The largest mean(s.d.) diameter of the common duct, after correcting for magnification, was 0·96(0·27) cm before cholecystectomy and 1·16(0·29) cm after surgery ($P<0\cdot0001$)*. Thirty-one of the 35 patients showed increased duct size after cholecystectomy, and the difference was 1 mm or more in 26 patients. There was a positive correlation between the increase in bile duct size and the time interval after cholecystectomy. After cholecystectomy a small but significant increase in bile duct diameter is demonstrable on ERCP.*

Keywords: Cholecystectomy, bile duct dilatation, endoscopic retrograde cholangiopancreatography

Whether the common bile duct dilates after cholecystectomy is controversial. In 1887 Oddi suggested that it does, to take over the reservoir function of the gallbladder[1]. Animal experiments in dogs supported this view[2,3]. The mean diameter of the common bile duct, as measured by ultrasonography, was 0·41 cm in normal subjects and 0·77 cm in postcholecystectomy patients[4]. However, two prospective studies found no ductal dilatation on ultrasonography of patients before and after cholecystectomy[5,6].

Bile duct dilatation is the cardinal sign of biliary obstruction[7]. An increase in the diameter of the common bile duct after cholecystectomy has important implications regarding the interpretation of imaging investigations in the cholecystectomized patient. We conducted a prospective evaluation of the common duct diameter before and after cholecystectomy using endoscopic retrograde cholangiopancreatography (ERCP).

Patients and methods

Patients admitted for cholecystectomy at the Prince of Wales Hospital routinely undergo ERCP as part of a prospective study evaluating the role of routine ERCP before cholecystectomy. Patients with a normal common duct on the preoperative cholangiogram had cholecystectomy without operative cholangiography. Forty-three patients, who were asymptomatic after the cholecystectomy, agreed to undergo repeat ERCP 140–400 days after the operation. All 43 patients had gallstones without common duct stones and underwent uneventful cholecystectomy without common duct exploration.

Preoperative and postoperative ERCP were performed in an identical manner by one of two endoscopists using an Olympus JF-1T duodenoscope (Olympus Optical Co. Ltd., Tokyo, Japan) (outer diameter 0·11 cm). Premedication consisting of pethidine (25–50 mg), Diazemuls® (KabiVitrum, Stockholm, Sweden) (5–10 mg) and Buscopan® (Boehringer Ingelheim, Ingelheim, FRG) (40 mg) was given intravenously immediately before the procedure. The contrast material used was Conray® 280 (May and Baker, Dagenham, UK). Radiographs were taken with an undercouch tube with the patient in the semiprone position immediately after adequate opacification of the biliary tree as seen with the aid of an image intensifier. Only films with adequate filling of the tertiary branches of the intrahepatic ducts were considered adequate for the purpose of this study. The widest diameter of the common hepatic duct or the common bile duct was measured on the radiograph with a pair of calipers and estimated to the nearest 0·1 mm. The diameter of the endoscope 1 cm proximal to the bending section was also measured on the same radiograph. The magnification of the common duct on the radiograph was compensated for by factoring down according to the magnification of the endoscope using the following formula:

$$\text{Actual diameter of bile duct} = \text{Measured diameter of bile duct} \times \frac{\text{Actual diameter of endoscope}}{\text{Measured diameter of endoscope}}$$

The corrected bile duct diameters before and after cholecystectomy in the same patient were compared using Student's paired t test. The correlation between the percentage increase in bile duct size with time after surgery was assessed by Pearson's correlation coefficient.

Results

Of the 43 patients who underwent preoperative and postoperative ERCP, films were studied in 35. The common bile duct could not be cannulated in five patients, the films were lost in one patient, and the tertiary branches of the intrahepatic ducts were not filled in the other two. After removal of the gallbladder and the cystic duct the landmark between the common hepatic duct and the common bile duct is lost. We therefore measured the greatest diameter of the common duct without specifying whether it was the common bile duct or the common hepatic duct. The mean(s.d.) diameter of the common duct increased from 0·96(0·27) cm before cholecystectomy to 1·16(0·29) cm after cholecystectomy ($P<0\cdot0001$). Thirty-one of the 35 patients had increased bile duct size after cholecystectomy, and the difference was 0·1 cm or more in 26 patients. In two patients the bile duct remained the same size, and in two patients the bile duct diameter was 0·13 cm and 0·06 cm smaller in the postoperative ERCP film. There was a positive correlation between the increase in bile duct size after surgery and the time interval after cholecystectomy (Pearson's correlation coefficient = 0·42, $P<0\cdot02$) (*Figure 1*).

Discussion

The diameter of the common bile duct differs when measured by different imaging techniques[8,9]. The common duct is bigger in radiographic studies because of magnification[9], the degree

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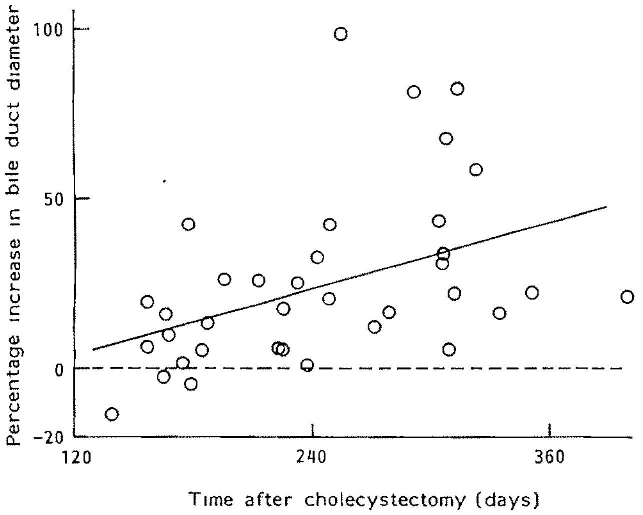

Figure 1 *Progressive increase in bile duct diameter with time after cholecystectomy* ($r=0{\cdot}42$, $P<0{\cdot}02$)

of magnification depending on the distance between the X-ray tube, the common bile duct and the X-ray plate. Techniques which involve direct introduction of contrast material into the common bile duct (percutaneous transhepatic cholangiography, operative cholangiography, ERCP, T tube cholangiography) may increase the diameter of the bile duct due to distension by the injected material under pressure[9]. In intravenous cholangiography the chloretic effect of the intravenous contrast may also cause distension[8]. The upper limit of normal common duct diameter is 1·0–1·1 cm for both percutaneous transhepatic cholangiography and ERCP[8]. Ultrasonography is more physiological but may represent an underestimate of the bile duct size as the echoes reflected from the duct wall may decrease the measurement of the lumen[9]. As the lower common duct is often obscured by duodenal gas, ultrasonography often measures the common hepatic duct instead of the common bile duct. Measurement of the bile duct at different sites may also be an important cause of the discrepancy between the sonographic and radiographic measurements[9]. With ultrasonography a common hepatic duct diameter of 0·4 cm is taken to be the borderline between the normal and the dilated[8].

Despite experimental evidence in dogs[2,3] that the bile duct dilates, presumably to assume the reservoir function of the gallbladder after cholecystectomy, measurement of bile duct diameter in humans before and after cholecystectomy has failed to demonstrate ductal dilatation. Le Quesne *et al.* measured the diameter of the common bile duct on operative cholangiography during surgery and on intravenous cholangiography 12 or more months after the operation. No evidence of common duct dilatation after cholecystectomy was found[10]. Two prospective studies using grey scale ultrasonography also failed to show any ductal dilatation after cholecystectomy[5,6]. These studies not only had difficulties in standardizing the measurements but also included many patients with common duct stones who underwent duct exploration and other procedures, which may affect the diameter of the duct. Edmunds *et al.*[11] studied 60 postcholecystectomy patients, none of whom had common duct exploration. Intravenous cholangiography was performed in the early postoperative period, and then 5–7 years later. The size of the common duct remained unchanged in eight patients, was smaller in 19 patients, and became larger in 33 patients. The incidence of biliary symptoms was, however, higher in those with bile duct dilatation and the group may have included patients with bile duct pathology.

We studied patients who only had gallbladder stones and no common duct pathology. They all had elective cholecystectomy without interference of the common bile duct. None had postcholecystectomy symptoms. Identical techniques of ERCP were used before and after cholecystectomy. A highly significant increase in bile duct diameter was demonstrated after cholecystectomy. The bile duct is capable of acute distension over a short period[12]. The apparent dilatation after cholecystectomy may be caused by distension of the biliary tree from injection of contrast during ERCP. The loss of the reservoir function of the gallbladder after cholecystectomy may lead to greater ductal distension on injection of the contrast. Indeed, Chang *et al.*[13] found that the performance of ERCP alters the bile duct diameter significantly, and that the increase in bile duct diameter is more marked in patients who have had their gallbladders removed. However, we believe that the observed postcholecystectomy bile duct dilatation is not an artefact because the dilatation increases with time (*Figure 1*). If distension alone caused such dilatation in our study, the percentage increase in bile duct diameter would not show such a positive correlation with the interval after surgery. The progressive increase in bile duct size after cholecystectomy is probably physiological because the volume and composition of bile are changed after cholecystectomy[14,15]. In conclusion, the ERCP findings of dilated common bile ducts in eight cholecystectomized patients need to be interpreted with caution.

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Pathogenesis of acute cholecystitis after gastrectomy

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The increased incidence of gallbladder diseases after gastrectomy is discussed with regard to contractile motility of the gallbladder. Ultrasonographic findings and contraction of the gallbladder in response to egg yolk or caerulein were studied before and after gastrectomy at intervals ranging from 2 weeks to 6 months. Enlargement of the gallbladder with accumulation of biliary sludge and hypomotility were frequently observed within a month of operation for gastric cancer, suggesting that biliary stasis is an important contributing factor in postoperative acute cholecystitis. Within 3 months of operation, contraction had recovered to close to preoperative levels and the incidence of biliary sludge formation gradually decreased. Daily administration of an opiate antagonist, naloxone (0·8 mg), significantly improved gallbladder dyskinesia and decreased the incidence of biliary sludge formation within 1 month of gastrectomy.

Keywords: Postoperative acute acalculous cholecystitis, gallbladder contraction, naloxone, denervation supersensitivity

Acute acalculous cholecystitis may have a more fulminant course than acute calculous cholecystitis with early appearance of gangrene and perforation. It may develop after abdominal surgery, and in the USA is reported particularly after operations on the colon[1,2]. However, including our own patients, more than 60 per cent of cases of acute acalculous cholecystitis in Japan developed after gastrectomy for gastric cancer[3,4]. The clinical course and management of seven patients in our institution who developed acute acalculous cholecystitis after gastrectomy during the last decade have been reviewed. As impaired gallbladder motor function after surgery has been proposed as an aetiological factor[5], ultrasonographic findings and gallbladder motility have also been studied before and after operation in patients undergoing gastrectomy for benign and malignant disease.

Patients and methods

Acute cholecystitis after gastrectomy

The records were reviewed of all patients with the diagnosis of acute cholecystitis following gastrectomy who were dealt with in our department between January 1977 and December 1988 Of 1096 patients who had undergone gastrectomy for gastric cancer, seven had developed acute cholecystitis.

Contractile motility of the gallbladder after gastrectomy

Seven healthy control subjects (mean age 50 years), 15 patients with gastric ulcer (mean age 55 years) and 62 patients with gastric cancer (mean age 61 years) were studied The gastric ulcer patients consisted of nine patients undergoing Billroth I gastrectomy and six undergoing a Billroth II procedure None of these patients with benign diseases had vagotomy and care was taken to preserve the hepatic branches of the left gastric artery. Gastric cancer patients had either subtotal (Billroth I, $n=18$, Billroth II, $n=17$) or total gastrectomy ($n=27$), including radical lymph node dissection and division of the vagal nerves around the oesophagus and the sympathetic nerves from the coeliac ganglion; however, the pancreas and spleen were left intact. The gallbladders of these gastric cancer patients had no evidence of malignant invasion. The mean period of total parenteral nutrition after gastrectomy was 4·5 days (range 3–8 days)

As previously described[5,6], contractile motility of the gallbladder following oral administration of 13 g dried egg yolk (Daiyan, Maruishi, Osaka, Japan) or intramuscular injection of 0·3 μg/kg caerulein (Kyowa Hakko, Tokyo, Japan) was studied by a real-time ultrasonography (Aloka SSD-256, Tokyo, Japan) before and after the operation Postoperative tests were performed at 2 weeks and at 1, 3 and 6 months after operation The presence of biliary sludge or stones was noted The gallbladder was visualized through a right subcostal space and angled to obtain images showing the largest longitudinal diameter. Tracing the gallbladder wall circularly enabled calculation of gallbladder area[5,6]. As we have previously shown that naloxone (0·4 mg) significantly improved the hypomotility of egg yolk-induced contraction 1 month after operation for gastric cancer[5], the effects of this opiate antagonist on caerulein-induced contraction was also studied. This study was performed in 15 gastric cancer patients who had undergone subtotal or total gastrectomy and was conducted both with and without naloxone premedication (Sankyo, Tokyo, Japan) Naloxone (0 4 mg) was injected intramuscularly at the same time as caerulein administration.

As naloxone improved the hypomotility of caerulein-induced contraction 1 month after the operation for gastric cancer, it was intramuscularly administered daily from the second to third week after the gastric cancer operation, to test the potential therapeutic value of naloxone. Differences between means were evaluated by Student's t test and regarded as significant if $P<0·05$. Values are expressed as mean(s e.) unless otherwise stated.

Results

Acute cholecystitis after gastrectomy

Of 1096 patients undergoing gastrectomy for gastric cancer, seven patients developed acute cholecystitis. Six of the seven patients were diagnosed as having acute cholecystitis at operation; in one patient the diagnosis was made on ultrasonography. No case of cholecystitis was seen after 379 gastrectomies for gastric ulcer Of the seven patients, six were men; the average age was 63·1 years (range 51–70 years). Cholecystitis had developed an average of 20 days after the operation (range 5–70 days). In five of the seven patients symptoms had developed within a month of gastrectomy. Oral intake had been resumed in six of the patients when the symptoms of cholecystitis developed. One patient was receiving parenteral nutrition No patient was found to have stones in the gallbladder or common bile duct. Bile peritonitis due to perforation or gangrene of the gallbladder was found in five patients. Cholecystectomy and peritoneal drainage were performed in six patients and percutaneous transhepatic gallbladder drainage was performed in one patient; four of the seven patients died.

Contractile motility of the gallbladder after gastrectomy

Egg yolk and caerulein caused a distinct contraction of the gallbladder in healthy subjects or preoperative patients; the

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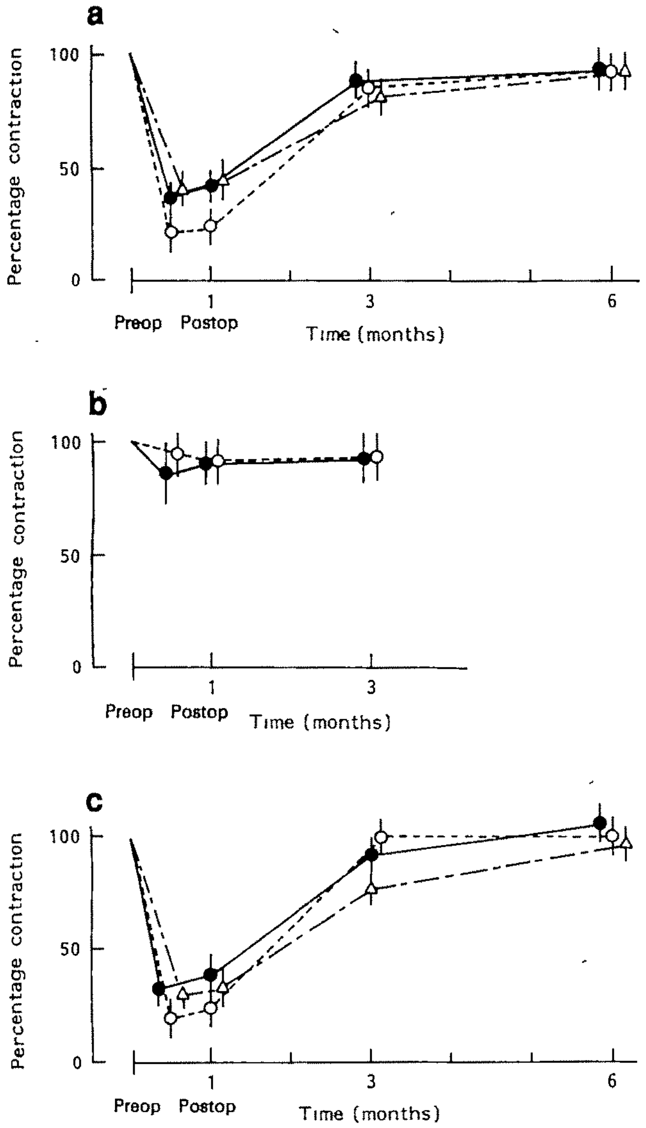

Figure 1 *Egg yolk-induced maximum contractile rate of the gallbladder after subtotal (Billroth I ●—●, Billroth II ○—○) or total gastrectomy (△—△) in patients having operation for* **a** *gastric cancer (Billroth I, n=7–11, Billroth II, n=7–10, ρ+double tract, n=12–15),* **b** *gastric ulcer (Billroth I, n=6–9, Billroth II, n=4–6); and* **c** *caerulein-induced maximum contractile rate of the gallbladder in patients with gastric cancer (Billroth I, n=4–6, Billroth II, n=7–10, ρ+double tract, n=5–8) Preoperative egg yolk or caerulein-induced maximum contractile rate was taken as 100 per cent. Not all patients had studies conducted at each interval; this accounts for the varied value of* n *in each subgroup*

maximum contractile rate was noted at 20 min and 40 min respectively after the administration of caerulein and egg yolk[5,6]. Egg yolk-induced maximal contractile rate of the gallbladder was significantly reduced 2–4 weeks after gastrectomy for gastric cancer (*Figure 1a*). On the other hand, egg yolk-induced contraction was not significantly reduced after gastrectomy for benign disease (*Figure 1b*). Gallbladder area in the fasting state was remarkably enlarged 2–4 weeks after operation for gastric cancer. The incidence of biliary sludge formation was significantly increased to a peak of 31 per cent at 1 month after operation (*Table 1*).

Egg yolk-induced contraction was more markedly reduced within 1 month of operation in patients who had undergone Billroth II gastrectomy for malignant disease than in those who had undergone Billroth I or total gastrectomy (*Figure 1a*) By 3 months after operation egg yolk-induced contraction had recovered to approximately the preoperative level and the incidence of biliary sludge formation also gradually decreased (*Table 1*). In three patients with gastric cancer, biliary sludge had been replaced by small stones (3–5 mm in diameter, with acoustic shadowing). Gallbladder wall thickening (more than 3 mm) was observed in only three patients within 1 month of the operation, despite the dysfunction of the gallbladder (*Table 1*).

Caerulein-induced contraction in gastric cancer patients was also significantly reduced 2–4 weeks after the operation, recovering to near preoperative levels more than 3 months after the operation There were no statistical differences in gallbladder contraction among Billroth I, Billroth II and total gastrectomy patients (*Figure 1c*) Naloxone (0·4 mg), despite its lack of effect on maximum contractile rate in healthy subjects or preoperative patients, significantly improved the hypomotility of gastric cancer patients 1 month after the operation (*Table 2*). Daily administration of naloxone (0·8 mg, from the second to the third week) also significantly improved the abnormal response to caerulein in patients with gastric cancer (*Table 3*). The incidence of biliary sludge formation was decreased from 42 per cent (five of 12 patients) by the second week to 17 per cent

Table 2 *Effects of naloxone (0·4 mg) on the maximum contractile rate of the gallbladder in response to caerulein in healthy subjects and gastrectomized patients with gastric cancer*

	Without naloxone	With naloxone
Healthy subjects ($n=7$)	67·3(3·0)	65·2(4 2)
Gastrectomized patients ($n=15$*)	18·3(7·7)	30·4(6 4)†

Values are mean(s e) Caerulein-induced contractions with and without naloxone were studied 1 month after operation. * Four patients with Billroth I, seven patients with Billroth II and four patients with total gastrectomy; † $P<0\ 05$

Table 1 *Ultrasound evaluation and contractile motility of the gallbladder before and after gastrectomy in 62 patients with gastric cancer*

	Before operation	Time after operation (months)			
		0·5	1	3	6
Fasting area, mean(s.e) (cm²)	12·5(1·6)	18 6(3·0)	19 0(4 0)	15 6(4 0)	15 4(4·2)
Wall thickness <3 mm	0	3 (5)	3 (5)	2 (3)	2 (3)
Biliary sludge	0	18 (29)	19 (31)	12 (19)	10 (16)
Stone formation	0	0	0	2 (3)	3 (5)
Maximum contractile rate, mean(s e.)					
To egg yolk	43·5(5·5)	18·5(4·3)	21 3(5 9)	42·7(6 3)	44 8(7·1)
To caerulein	67 3(8 1)	21·6(6 0)	23·2(7 2)	58 3(7 2)	59 6(8·2)

Values are given as number of patients with percentages in parentheses unless otherwise stated Eighteen patients with Billroth I, 17 patients with Billroth II and 27 patients with total gastrectomy of Roux-en-Y reconstruction (side-to-end anastomosis between ρ-shaped jejunal pouch and oesophagus, with side-to-end jejunoduodenostomy)[7]

Table 3 *Effects of daily administration of naloxone (0·8 mg for 7 days) from the second to third week after gastrectomy on caerulein-induced contraction in patients with gastric cancer*

	Second week	Third week
Without naloxone ($n=10$)	28·5(5·6)	31·0(6·2)
With naloxone ($n=12$*)	29·7(6·2)	49·7(7·0)†

Values are mean(s.e.). Preoperative caerulein-induced gallbladder contraction was taken as 100 per cent. * Three patients with Billroth I, four patients with Billroth II and five patients with total gastrectomy, † $P<0·05$

(two of 12 patients) by the third week by daily administration of naloxone.

Discussion

In our experience the incidence of acute acalculous cholecystitis after gastrectomy for gastric cancer was 0·64 per cent (seven patients of 1096 cases), making it an uncommon complication. However, obvious enlargement of the gallbladder area with the accumulation of biliary sludge was frequently observed at ultrasonography within a month of operation for gastric cancer but not for gastric ulcer or colon cancer[5]. Glenn and Wantz[8] claimed that biliary stasis was an important precipitating factor in postoperative acute acalculous cholecystitis. As in our patients, postoperative acute cholecystitis is commonly reported to develop within a month of operation[1–4], coinciding with a period of significant hypomotility of the gallbladder.

It remains unclear why gallbladder motility might be impaired in the month following gastrectomy for gastric cancer. As the contraction in response to egg yolk was not reduced after simple gastrectomy for gastric ulcer, it seems likely that the radical lymph node dissection (and associated vagotomy and sympathectomy) undertaken in gastric cancer is implicated. Numerous investigators have reported that truncal vagotomy produces atony of the gallbladder and bile duct[9,10]. Fried *et al.*[11] found that truncal vagotomy inhibited gallbladder pressure in response to fat without affecting plasma cholecystokinin (CCK) levels in dogs. Although they suggested that interruption of vagus-mediated reflexes between the intestine and gallbladder might be responsible, the possibility of decreased sensitivity of the gallbladder to CCK after truncal vagotomy has not been excluded. Although CCK is believed to act on the gallbladder muscle cells and not on the cholinergic neurons, recent *in vivo* experiments[12–14] oppose this theory by showing that CCK-stimulated contraction was significantly reduced by atropine. Behar and Biancani[14] proposed that CCK receptors were present on both the muscle cells and cholinergic neurons of the cat gallbladder. With respect to human gallbladder contraction, egg yolk, caerulein and CCK-induced *in vivo* contractions were almost completely abolished by atropine premedication, suggesting that CCK receptors located on cholinergic neurons are more important than those on the muscle cells.

Our present study showed that naloxone, an opiate receptor antagonist, which has no effect on caerulein-induced contractions in healthy subjects or preoperative patients, significantly improved the hypomotility of the gallbladder 1 month after operation for gastric cancer. Enkephalin immunoreactivity has been detected in the digestive system, including the gallbladder[15], and is localized in nerves of the myenteric plexus. It is possible, therefore, that vagotomy and sympathectomy as a result of radical lymph node dissection might increase the opiate receptor affinity (i.e. denervation supersensitivity)[16] of the intramural nerve plexus of the gallbladder. Denervation supersensitivity has been invoked to explain the increase in the total number of receptors after denervation. The number of acetylcholine receptors located at the neuromuscular junction begins to increase between 2 and 3 days after denervation, subsequently decreasing at 45 days[16]. Because the effects of CCK or caerulein on gallbladder contraction in healthy subjects were antagonized by opiates[1,7], the increased opiate receptor affinity of the intramural plexus after denervation might decrease CCK-induced acetylcholine release from the cholinergic nerve terminals. Impaired gallbladder motility in response to egg yolk or caerulein noted within 1 month of operation gradually returned to close to normal 3 months later, suggesting a gradual decrease in the number of opiate receptors of the intramural plexus.

Daily administration of naloxone from the second to third week after operation remarkably improved the gallbladder dysfunction and decreased the incidence of biliary sludge formation, indicating a potential therapeutic use of this opiate antagonist.

The incidence of gallstone formation as a late complication of gastrectomy is reported as 13–42 per cent[18,19]. In our patients, three of 62 cases (5 per cent) developed gallstone formation from biliary sludge within 6 months of gastrectomy. Further study covering a longer period of observation is needed to clarify the mechanism of gallstone formation after gastrectomy, especially with regard to the relationship between gallstone formation and gallbladder motor function.

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Case report

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HELLP – it's not cholecystitis

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The acute abdomen in pregnancy poses a difficult diagnostic challenge to obstetrician and surgeon. We report details of a patient with the HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) manifesting as acute cholecystitis which progressed to severe pre-eclampsia requiring termination of pregnancy. It is unusual in the timing of presentation in the middle of the second trimester and highlights the importance of cooperation between both specialties.

Case report

A 27-year-old primagravida presented in the 20th week of an uncomplicated pregnancy with a 24-h history of vomiting and right upper quadrant pain radiating through to her back. She was apyrexial, tachycardic, and tender in the right upper quadrant with a positive Murphy's sign Her blood pressure (130/90 mmHg) was little different from her booking blood pressure (125/85 mmHg) She had a leucocytosis of 22.4 × 10^6/l but other investigations including urinalysis, urea and electrolytes and amylase were normal A clinical diagnosis of acute cholecystitis was made and she was started on intravenous ampicillin. Subsequent ultrasound scanning showed no gallstones and no other liver abnormality. The antibiotic was discontinued.

On the third day of her admission she developed bilateral pitting oedema and on day 4 she had proteinuria and a blood pressure of 160/110 mmHg There were no visual or neurological symptoms but her epigastric pain persisted. Her liver enzymes had risen, haemoglobin had fallen 2 g with evidence of haemolysis on the peripheral blood film; fibrin degradation products were raised and platelet count had fallen suggesting disseminated intravascular coagulation.

A diagnosis of pre-eclampsia was made and she was transferred to the obstetric unit where labour was induced with an extra-amniotic infusion of prostaglandin E_2 (Prostin E_2®, Upjohn Ltd , Crawley, UK). Following delivery the haematological and biochemical abnormalities returned to normal without further intervention (*Figure 1*).

Discussion

Acute abdominal pain in pregnancy is not uncommon and often poses a difficult diagnostic problem. In the last trimester of pregnancy pre-eclampsia may mimic hepatitis, cholecystitis and pyelonephritis[1–3]. The diagnosis is usually made by the presence of one or more of the accepted criteria hypertension 160/110 mmHg, proteinuria >5 g/24 h, oliguria <400 ml/24 h, cerebral or visual disturbances, or pulmonary oedema. To these criteria Weinstein added a syndrome characterized by haemolysis (H), elevated liver enzymes (EL) and low platelet count (LP) – the HELLP syndrome[4]. Its clinical manifestations include right upper quadrant pain and tenderness and vomiting. The patient becomes anaemic with evidence of microangiopathic haemolysis (schistocytes, polychromasia and burr cells on a peripheral blood film); the liver enzymes, in particular the alanine transaminase and aspartate transaminase are elevated and the platelet count falls The presence of disseminated intravascular coagulation signifies more extensive liver disease[5].

The pathological basis of the disease is unclear. Thrombocytopenia is due to increased consumption with increased megakaryocyte activity to compensate. The platelets adhere to areas of damaged vascular endothelium. Liver biopsy reveals fibrin deposition within the sinusoids and the obstruction to portal blood flow leads to liver enlargement It is the distension of Glisson's capsule which causes the right upper quadrant pain and liver rupture has been reported. The microangiopathic haemolytic anaemia is due to red cell fragmentation consequent upon passage through small blood vessels with intimal damage and fibrin deposition[6].

It is unusual for the HELLP syndrome to precede the other features of pre-eclampsia[3,7]. The authors are not aware of the condition presenting in isolation as early as the 20th week of gestation.

This case highlights the necessity for close cooperation between general surgeon and obstetrician Failure to recognize the characteristic features of the syndrome and institute appropriate treatment (the expeditious delivery of the fetus) may result in both fetal and maternal death[1,6,8].

Acknowledgements

We thank Mr P. D Milton, consultant obstetrician, for permission to report this patient.

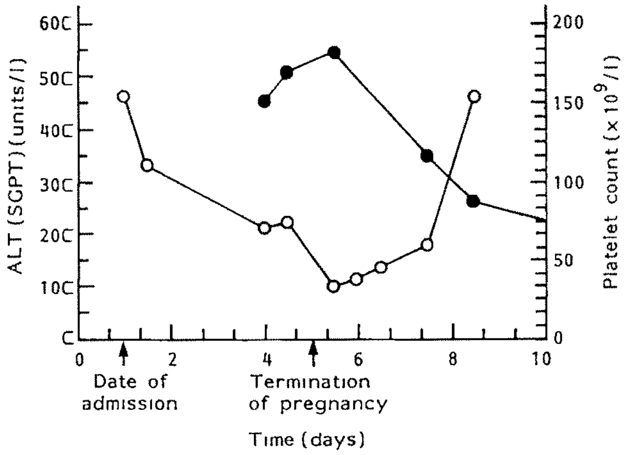

Figure *Liver enzyme alanine transaminase, ALT, or serum glutamic pyruvate transaminase, SGPT and platelet count variation during admission.* ●, *ALT,* ○, *platelets*

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Announcement

Royal College of Physicians of Glasgow

In common with the other Royal Colleges of Surgeons in the United Kingdom and Eire, the Royal College of Physicians and Surgeons of Glasgow proposes to introduce a new format for the Surgical Fellowship Examination (FRCGlasg). The Regulations for the new Examination are now available and may be obtained on request from the College Registrar. A precis of the Regulations is given below:

The Surgical Fellowship Examination will consist of an examination in the basic sciences (Part A) and an examination in surgery in general (Part B). The candidate may elect to take Part A separately from Part B or to take both Part A and Part B together in accordance with the undernoted Regulations.

Part A

Before admission to the examination a candidate shall be required to produce evidence satisfactory to the Council of: (1) holding a qualification recognized by the General Medical Council or the Council of the College; and (2) being qualified for not less than 2 years from the date of his/her Diploma of medical qualification.

The Part A examination will consist of: multiple choice question paper lasting for 3 hours and; an oral examination in anatomy.

Part B

Before admission to the examination a candidate shall be required to produce evidence satisfactory to the Council of having: (1) been successful in Part A or its equivalent, or having been exempted therefrom; (2) held a recognized medical qualification for not less than 4 years from the date of his/her Diploma of medical qualification; and (3) completed 2 years in addition to the preregistration year in clinical surgery posts recognized by the Council of the College.

The Part B examination will consist of: a written essay paper lasting for 3 hours duration on the subject of surgery in general and will include aspects of the principles and practice of surgery and surgical pathology; an oral examination in surgical physiology and principles of surgery and an oral examination in surgical pathology and operative surgery; and a clinical examination.

Further details about this examination and the examination in otolaryngology, along with a copy of the full regulations may be obtained from: The Registrar, Royal College of Physicians and Surgeons of Glasgow, 234–242 St Vincent Street, Glasgow G2 5RJ, UK.

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Management of the stump of the pancreas after distal pancreatic resection

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The optimal management of the stump of the pancreas following distal resection remains controversial. To determine whether there was an advantage in draining the stump of the pancreas into a Roux-en-Y loop of jejunum, a retrospective survey of 113 patients who had a distal pancreatectomy for chronic pancreatitis or complications of acute pancreatitis in the non-acute phase was undertaken. The decision to perform a drainage procedure was determined on the basis of the pancreatogram, the size of the pancreatic duct and technical factors at the time of the operation. Sixty-seven patients had no drainage procedure and 46 patients had a drainage procedure. The two groups were comparable in all respects before surgery. The postoperative outcome in the short- and long-term was similar in both groups. It is concluded that caudal pancreatic drainage confers no benefit following distal pancreatic resection.

Keywords: Chronic pancreatitis, pancreatic drainage, pancreatic resection

Resection of the body and tail of the pancreas can be a useful and successful procedure in the management of patients with chronic pancreatitis or complications of acute pancreatitis such as pseudocysts, pancreatic duct disruption, duct strictures, abscess or pre-resection haemorrhage. Despite several descriptions of of the operative procedure[1–5] there is no consistent description of the technique used to manage the cut end of the pancreas, although several variants have been suggested[1,3]. Over the years our preferred technique has been to drain the stump of the pancreas into a Roux-en-Y loop of jejunum, as it was considered less likely to give rise to complications, particularly fistula formation. In order to determine if formal jejunal drainage is beneficial, a comparison has been undertaken between the patients who had jejunal drainage and those who had the stump sutured.

Patients and methods

Between May 1976 and June 1988, 128 patients underwent distal pancreatic resection for chronic pancreatitis. In seven cases the distal resection completed a total pancreatic resection and these patients are excluded from this study Eight other patients were excluded from the study because of inadequate data. All information has been retrieved from our computer database that is maintained on a prospective basis Thus the 113 patients considered here have had a primary distal pancreatic resection.

Patients

The 113 patients studied have been subdivided according to the methods of management of the cut end of the pancreas; the drainage group had caudal pancreatic ductal drainage and comprised 46 patients and the non-drainage group comprised 67 patients

Operative procedure

A standardized technique of distal pancreatectomy was employed in which the extent of resection was taken to a centimetre to the right of the portal vein A concomitant splenectomy was performed in all but one patient. In patients who had a drainage procedure a 40-cm long Roux-en-Y loop of jejunum was constructed and the cut end of the pancreas was anastomosed to the side of the jejunum along its antimesenteric border with a direct mucosa to pancreatic duct anastomosis performed with fine non-absorbable suture material In the non-drainage group, the pancreatic duct was closed with 4/0 Prolene® (Ethicon Ltd , Edinburgh, UK), and the stump sutured with interrupted braided polyamide initially and more recently with polydioxanone The decision to undertake a drainage procedure was made at the time of resection and was determined by the size of the duct (the assessment taking into consideration the findings on pancreatography performed endoscopically or percutaneously) and by the ease with which the duct was identified at operation. All patients in whom the duct was identified at the point of transection underwent a drainage procedure during the early part of our experience, and a stent was placed across the anastomosis Drainage was not undertaken if the duct was embedded in a mass of fibrous tissue. In all patients resection of the distal pancreas left behind a patent pancreatic duct in the head of the pancreas All patients had small calibre suction drains placed adjacent to the anastomosis or site of closure of the pancreatic stump Amylase levels of the drain contents were measured to identify the presence of a fistula which was inferred if the drainage from the suction drains lasted for 7 days, and if the amylase content of the draining fluid was greater than 3000 units/l.

Parameters assessed

In order to determine that there was no bias between the groups other than the operative findings, the following factors were determined· age, sex, presenting symptoms, aetiology, operative features in terms of the length of operation and blood loss.

The presenting features incorporated an assessment of the severity of the underlying pancreatitis Pain was assessed in terms of analgesic requirement. As these patients were followed up closely in a specialist pancreatic clinic, long-term analgesic requirement both in terms of the type of drug used and the dosage required were documented. Severity of pain was assessed by a specialist pancreatic clinic nurse who was not aware of the nature of the stump closure The severity of pain has been graded as follows: 0, no pain; 0a, some pain but no analgesic required, 1, pain controlled by Panadol® (Winthrop Laboratories, Guildford, UK) or Distalgesic® (Dista Products Ltd, Basingstoke, UK), and 2, pain controlled by pentazocine or pethidine

Complications of pancreatitis were identified before surgery on clinical and radiological grounds. Ultrasonography, endoscopic pancreatography and computed tomographic scanning were undertaken routinely Other tests were undertaken where appropriate. Routine biochemical tests were performed including assessment of hepatic function in all patients before and after surgery.

Early deaths were those occurring within 30 days of the operation while late deaths occurred after 30 days Late deaths were further subclassified into those related to the pancreatic operation and those that were due to incidental causes.

The postoperative complications studied were sepsis (which included wound, respiratory and indwelling catheter related infections), pancreatic leaks and haemorrhage (subdivided into minor and major haemorrhage) Wound infection was defined as erythema extending over 5 mm from the wound edges with or without discharge of pus. Respiratory sepsis was defined as cough with expectoration associated with pyrexia and positive sputum culture. Indwelling catheter-related

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Table 1 *Comparison of presenting features in the drainage group and the non-drainage group*

Presenting feature	Drainage (*n*)	Drainage (%)	Non-drainage (*n*)	Non-drainage (%)
Pain	46	100	67	100
Narcotic use	18	39	28	42
Initial acute pancreatitis	17	37	28	42
Recurring acute attacks	24	52	36	54
Complications of pancreatitis				
Diabetic	9	20	10	15
Steatorrhoea	10	22	12	18

sepsis was identified by an increase in white blood count, pyrexia and culture of organisms from the catheter tip or a positive blood culture Catheter-related sepsis was confirmed by subsidence of signs with the removal of the line A major haemorrhage was defined as a drop in haemoglobin concentration ≥4 g/dl with a transfusion requirement of >4 units packed cells at resuscitation, and evidence of peripheral circulatory impairment. A minor haemorrhage was defined as evidence of haemorrhage with minimal or transient circulatory embarrassment.

Outcome after distal pancreatic resection has been analysed in all patients, assessing the incidence of postresection pain, the number of hospital readmissions and the incidence of subsequent progression to total pancreatic resection because of failure to control the patient's symptoms. The postresection exocrine status (defined as the presence of clinical steatorrhoea requiring enzyme supplementation) and endocrine status (defined as clinical glucose intolerance requiring insulin) has also been compared between the two groups

Statistics

The Mann–Whitney *U* test, Fisher's exact test and the χ^2 test have been used where appropriate.

Results

Age and sex distribution

The drainage group comprised 28 men and 18 women with median ages at presentation of 36 years (range 18–70 years) and 39 years (range 9–67 years) respectively The interval between the onset of disease and operation in both groups was a median of 4 years. In the group of patients with no drainage procedure there were 47 men and 20 women with median age of 40 years (range 15–65 years) and 33 years (range 6·5–51 years) respectively. The interval between the onset of disease and operation was a median of 3·8 years.

Presentation

The severity of the underlying pancreatitis as assessed by the presenting symptoms is shown in *Table 1*. Pain was the dominant indication for resection and was present in all patients Regular narcotic analgesic intake was recorded in 39 per cent of patients in the drainage group and 42 per cent in the non-drainage group. In 37 per cent of patients in the drainage group and 42 per cent of patients in the non-drainage group acute pancreatitis was present at initial presentation. Recurring attacks of severe pancreatic pain requiring hospital admission occurred in 52 per cent of the former and 54 per cent of the latter. A study of the complications of pancreatitis showed that 23 of 46 patients (50 per cent) in the drainage group and 48 of 67 patients (72 per cent) in the group without drainage had suffered complications of pancreatitis (pseudocysts, pancreatic abscess, pancreatic phlegmon, fistulae and preresection haemorrhage).

Ductal anatomy

Pancreatography revealed a ductal abnormality as defined by duct strictures, disruptions and calculous obstruction in 17 patients in the drainage group and 34 patients in the non-drainage group. Pancreas divisum was present in five patients in each group.

Aetiology

The cause of pancreatitis in 17 patients in the drainage group and 22 patients in the non-drainage group was unknown. Many of the 39 patients with no known cause were initially investigated for alcoholism but a careful social and family history excluded it. However, 17 patients (40 per cent) in the former and 22 in the latter group (33 per cent) had alcoholic pancreatitis. The miscellaneous group includes patients with hyperlipidaemia, mumps, pancreatitis, drug induced pancreatitis and patients in whom the initial episode of pancreatitis was attributed to gallstone disease. Pancreas divisum was the cause in five patients in each group and in one patient the pancreatitis was related to trauma, while in other patients the aetiology has been multifactorial.

Operative data

The length of time taken to perform the distal pancreatic resection with splenectomy in the two groups of patients was mean of 3·9 h (range 2·5–5·5 h) in the drainage group compared with 3·1 h (range 2–6·5 h) in the non-drainage groups. Although these differences were not significant ($U = 0{\cdot}465$), avoiding drainage does appear to save time. The operative blood loss in the drainage group was a mean of 1·6 litres (range 0·1–6 litres) and that in the non-drainage group was 2·02 litres (range 0·25–6·5 litres). These differences were not significant.

Postoperative data

The postoperative stay in hospital was a median of 20 days (range 10–98 days) in the drainage group, and 17 days (range 10–84 days) in the group of patients with no drainage procedure. There was no difference between the two groups ($U = 0{\cdot}497$). Fourteen patients in the drainage group and 11 patients in the non-drainage group spent over 1 month in hospital after surgery.

Operative complications

There were septic complications in 13 patients in the drainage group and 19 patients in the non-drainage group (*Table 2*). No patients developed a subphrenic collection. There was no significant difference in the incidence of pancreatic leaks or postresection haemorrhage between the two groups.

Mortality

The only early death occurred in a man aged 46 years (non-drainage group) who died of myocardial infarction on the seventh postoperative day.

There were four late deaths in the group of patients who underwent a drainage procedure, of whom one patient died of hypoglycaemia 2 years after resection and three patients died of non-pancreatic causes: suicide (one case), AIDS (one case) and pneumonia (one case). All three late deaths in the non-drainage group were due to non-pancreatic causes (cerebrovascular accident (one case), aortic aneurysm repair

Table 2 *Postoperative complications following distal pancreatectomy with or without drainage*

	Drainage (*n*)	Drainage (%)	Non-drainage (*n*)	Non-drainage (%)
Overall	21	46	29	43
Sepsis	13	28	19	28
Wound	4	—	3	—
Respiratory	6	—	8	—
Catheter sepsis	3	—	5	—
Urinary/systemic	—	—	3	—
Pancreatic fistula	1	2	4	6
Haemorrhage	7	15	6	9

Table 3 *Late deaths following distal pancreatectomy*

Age (years)	Cause of death	Length of time after resection (years)
Drainage group		
41	Hypoglycaemia	2
46	AIDS	2
46	Suicide	8
65	Pneumonia	2
Non-drainage group		
54	Cardiovascular accident	10
62	Aortic aneurysm	2
63	Carcinoma of breast	2

Table 4 *Comparison of the severity of pain following distal pancreatectomy with or without drainage*

	Drainage		Non-drainage	
Severity of pain	(*n*)	(%)	(*n*)	(%)
0	23	79	32	68
0a	2	7	2	4
1	2	7	2	4
2	2	7	11	24
Inadequate data	17	–	20	–

(one case), carcinoma of the breast (one case). The interval between resection and late death is shown in *Table 3*.

Eventual outcome

Pain. The two groups did not differ significantly with regard to the severity of postresection pain (*Table 4*).

Progression to total pancreatectomy. Of the 27 patients who progressed to total pancreatic resection uncontrolled pain was the indication for complete resection in all cases; 14 of these patients (52 per cent) had had a previous distal resection with caudal drainage while 13 patients (48 per cent) had had a resection with closure of the pancreatic stump.

Hospital readmissions. The two groups did not differ significantly in terms of the frequency of hospital readmission (*Table 5*).

Morbidity Diabetes was present in 15 patients following pancreatic resection in the drainage group and in 13 in the non-drainage group; six further patients in each group had steatorrhoea requiring enzyme supplementation after pancreatic resection.

Follow-up. Patients were followed up in our pancreatic clinic at intervals of a maximum of 1 year The period of follow-up was a median of 2 years (range 1–10 years) in the drainage group and 3 years (range 1–11 years) in the non-drainage group. Patients who subsequently progressed to total pancreatectomy have been included in the analysis of outcome (*Tables 3* and *4*). All patients had been contacted, but in some it was difficult to assess in detail their pain and their number of readmissions, hence these patients have not been included in *Tables 4* and *5*.

Discussion

The two groups of patients in our study were comparable in terms of age, sex, distribution, length of history, presenting features and aetiology. There was no statistically significant difference in the incidence of complications before resection despite the greater number of complications identified in patients in the non-drainage group The incidence of ductal lesions discerned on pancreatography were similar. The eventual outcome was similar in the two groups.

The surgical objective of draining the cut surface of the pancreas is to avoid the effects of a leak from the pancreatic stump and to achieve better drainage by enabling the pancreatic juice to escape both proximally and distally. The standard technique of applying a Roux loop achieves this objective. During the early part of our experience, we routinely performed tubograms through splints placed across the anastomosis to demonstrate patency which was always present. The anastomosis, however, is often found to be occluded in patients undergoing re-exploration and the high stenosis rate may be reflected in failure to provide long-term relief[16].

Pancreatic pain has been thought to originate from a distended and inadequately draining duct Various operations have been devised to improve ductal drainage in the hope that this would reduce symptoms, although the mechanism by which this is achieved is unclear. Nevertheless, with the failure of coeliac plexus blockade[7] and the very limited success of left coeliac ganglionectomy[8], drainage has been the mainstay of the surgical relief of pain, short of resection. Such procedures have included Doubilet's operation of pancreatic transection with implantation of the cut ends into a Roux loop of jejunum[3]; DuVal's operation of caudal pancreatectomy with an end-to-side Roux-en-Y pancreaticojejunostomy[9], and longitudinal pancreatojejunostomy with or without associated pancreatic resection[10–12]. A comparison of the Duval operation undertaken in six patients, with the Thal-type longitudinal pancreatojejunostomy undertaken in 23 patients, by Jordan *et al.*[13] suggests that the latter procedure is superior in terms of both early and late results, but the groups are small and a bias towards the latter procedure cannot be ruled out. The operation of caudal pancreatectomy with drainage of the residual pancreatic duct into a Roux loop of jejunum was mentioned by Longmire *et al.*[1] in their experience of pancreatic resection in chronic pancreatitis, and was found by them to be of no value. Sarles *et al.*[14] undertook distal pancreatic resections in 23 patients of whom 14 underwent a drainage procedure. A critical assessment of the value of draining the stump of the pancreas is lacking. The inadequacy of surgical data is evident from the fact that no mention is made by Frey *et al.*[2] in their major series on distal pancreatic resection of the fate of the cut end of the pancreas. The lack of those important data makes it difficult to assess the influence of the drainage operation on the incidence of complications or outcome.

Duodenal and biliary obstruction are occasionally the source of considerable pain, especially in fibrosing pancreatitis and following resection of the pancreatic head. Such patients must be identified and treated before continuing pain is ascribed to continuing pancreatitis[15–18].

It is our experience that drainage offers no advantage in terms of operative blood loss, postoperative stay, complications or improvements in long-term results. As a result of this analysis, anastomosis of the cut end of the pancreas to jejunum or stomach should be abandoned, and the stump of the pancreas managed by a careful ligation of the duct with closure of the cut surface by interrupted sutures of a delayed absorbable material. Further, the use of pancreatojejunostomy for any

Table 5 *Comparison of the incidence of readmissions between the two groups*

	Drainage		Non-drainage	
No of readmissions	(*n*)	(%)	(*n*)	(%)
0	24	83	39	83
1	4	14	2	4
2–4	1	3	5	11
>4	–	–	1	2
Inadequate data	17	–	20	–

reason should be questioned; in this series the procedure failed to confer long-term benefit, and there were an equal number of failures in each group requiring total pancreatectomy. There is now good evidence that ductal drainage is valuable only when the duct is wider than 8 mm in diameter, and a longitudinal procedure is more effective than resection with distal drainage[19–20]. The conclusion of this study is that the pancreatic stump should be closed without drainage after distal pancreatic resection, and the need to ever perform a drainage procedure in the presence of an anatomically patent duct in the head of the pancreas is questioned

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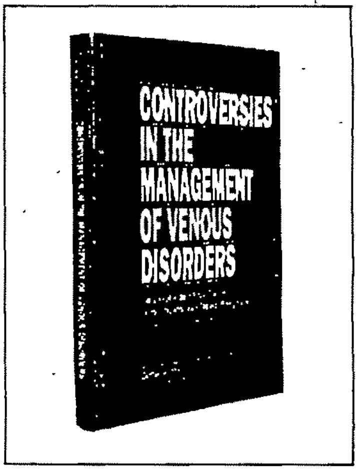

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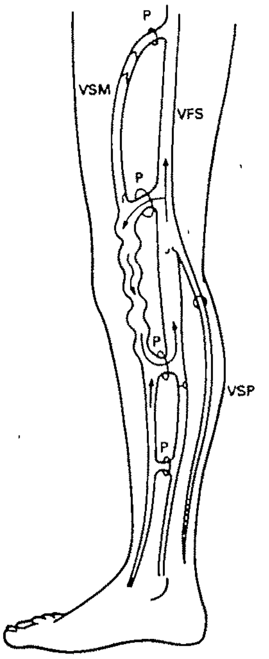

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Recurrent reflux and wrap disruption after Nissen fundoplication: detection, incidence and timing

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One hundred and twenty-five patients with refractory gastro-oesophageal reflux disease underwent floppy Nissen fundoplication. Median follow-up was 52 months, and included endoscopy, manometry and prolonged pH recordings in all cases in addition to clinical assessment. Using objective criteria, 12 patients (9·6 per cent) developed recurrent reflux. In nine of these patients, endoscopy had suggested that the Nissen fundoplication had disrupted; wrap disruption was confirmed in seven patients who underwent reoperation. The median time to endoscopic recognition of wrap disruption was 7 months (range 3–10 months). In contrast, of 115 patients with endoscopic evidence of an intact fundoplication, only 3 (2·6 per cent) had recurrent reflux. Endoscopy allowed reliable differentiation between those with and without reflux control after operation ($P<0{\cdot}001$)*. These results suggest that recurrent reflux after Nissen fundoplication is due to wrap disruption. This phenomenon occurs within the first postoperative year and can be recognized by informed endoscopic assessment.*

Keywords: Gastro-oesophageal reflux, Nissen fundoplication, recurrent reflux, timing, endoscopic assessment

Advances in our understanding of the pathophysiology of gastro-oesophageal reflux disease have resulted in a shift away from the anatomical hiatus hernia repairs such as that popularized by Phillip Allison[1] to more physiological antireflux operations. Currently the Nissen and Belsey fundoplications and their modifications[2–5] are the most widely used surgical techniques for treatment of refractory disease. The Hill posterior gastropexy[6] also has a small but enthusiastic following. While all of these operations can achieve good results, failures do occur both in terms of complications of the procedure and recurrent reflux disease. Our own preferred procedure is the floppy Nissen fundoplication[7]. Recurrent reflux has occurred in about 10 per cent of patients but the precise reasons for failure have not been clear.

Bushkin *et al.*[8] reported a series of 165 patients in which 13 (8 per cent) had symptoms of recurrent or persistent reflux. Only five patients were considered symptomatic enough to undergo reoperation at which time disruption of the fundoplication was found in four cases. Others have suggested that fundoplication disruption is the cause of recurrent reflux but have offered no objective evidence in support[9].

Donahue *et al.*[10] have described the endoscopic appearance of the intact Nissen fundoplication in a small group of patients, and suggested that this might be a useful form of assessment. The aim of the present study was to investigate the incidence of recurrent reflux and its relationship to dehiscence of the fundoplication. We also wished to establish when this was most likely to occur.

Patients and methods

One hundred and twenty-five consecutive patients (65 men; 60 women) with a median age of 52·5 years (range 25·1–79·4 years) were studied before and after Nissen fundoplication for refractory gastro-oesophageal reflux. All had received extensive medical treatment including combinations of H_2-receptor antagonists, antacid–alginate preparations, prokinetic agents and, in some cases, omeprazole. The median duration of symptoms before operation was 60 months (range 9–327 months). The diagnosis of reflux was confirmed by endoscopy or prolonged pH recording, the majority (113, 90·4 per cent) of patients undergoing both tests.

All patients had a 'floppy' Nissen fundoplication as described by Donahue and colleagues[7]. This consisted of a short (2–3 cm) circumferential fundoplication around an indwelling 50 Fr mercury bougie and a 16 Fr nasogastric tube. Six to eight 2/0 silk sutures were used for the wrap. After completion of the wrap a 36 Fr dilator or the equivalent sized finger could be passed easily between the plication and the oesophagus. Full mobilization of the fundus by division of the short gastric vessels was performed, and the hiatus was closed loosely behind the oesophagus. The majority of operations (78, 62 per cent) were performed by the abdominal route and 16 patients underwent an additional procedure at the time of fundoplication, either for concurrent peptic ulcer disease (11 patients) or cholelithiasis (five patients). Intraoperative trauma necessitated splenectomy in three cases (2·4 per cent), and one patient required thoracic re-exploration for postoperative bleeding. All operations were performed by, or under the direct supervision of, the senior author (J.B.). Follow-up was for a median of 52 months (range 6–110 months). Endoscopy, manometry and prolonged pH studies were performed in all patients 3–11 months after operation (median 7 months).

Oesophageal manometry was performed using low compliance equipment. Most patients were studied using a commercially available multilumen catheter (Arndorfer Medical Specialties, Greendale, Wisconsin, USA), which has an external diameter of 4·5 mm. A smaller number of patients were studied using another catheter (Synectics Medical AB, Stockholm, Sweden) with an external diameter of 3 mm. Both catheters were perfused with water from an Arndorfer pneumohydraulic pump at a rate of 0·6 ml/min. Pressure recordings were made from three radially spaced lumens, situated 5 cm from the catheter tip, and three more proximally placed ports at 5 cm intervals. The lower oesophageal sphincter (LOS) pressure was measured by a station pull-through technique, the accuracy and reproducibility of which has been previously reported from this laboratory[11]. The length of the LOS, above and below the pressure inversion point, was also measured.

Prolonged pH recordings were performed using an antimony-tipped pH electrode (Synectics Medical AB), positioned 5 cm above the LOS. Intraoesophageal pH was recorded on a solid state recorder (Digitrapper®, Synectics Medical AB) over a 24-h study period. The data were played back and analysed on a microcomputer, using a commercially available program (Gastrosoft®, Esophagram®, Synectics

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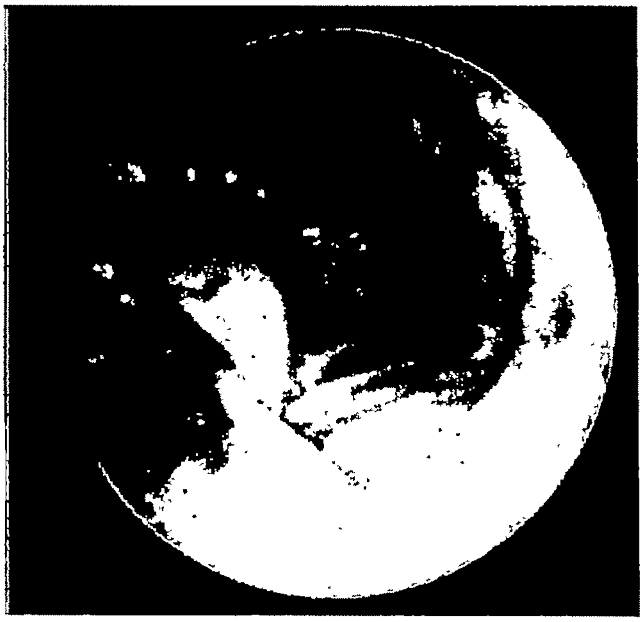

Figure 1 *Endoscopic view of the intact fundoplication as seen from below, showing the typical elevated fold appearance*

Medical AB). A number of earlier studies were performed using a glass pH electrode (Pye Unicam 140/E7, Cambridge, UK) and similarly analysed The pH results were interpreted using the criteria of Johnson and DeMeester[12]

Fibreoptic upper gastrointestinal endoscopy was performed in all patients by three experienced endoscopists. After operation, particular attention was given to the appearance of the cardia seen from below by retroflexion of the endoscope. The postfundoplication appearance was first reported by Donahue and colleagues[10], who described the 270° fold created by the fundoplication as being similar to an inverted cone with the apex extending into the oesophagus and one border continuous with the lesser curve of the stomach. We feel the term 'Nissen nipple' aptly describes this appearance (*Figure 1*).

Satisfactory reflux control was defined as complete resolution of all preoperative symptoms, absence of oesophagitis at endoscopy, and a normal 24-h pH recording at the postoperative assessment. All subjects gave fully informed consent with respect to both the investigative and operative procedures, and the methods were approved by the Ethical Committee of the Salford Health Authority Results were analysed by non-parametric statistical methods using the χ^2 test with Yates' correction for continuity and Wilcoxon's rank sum test where appropriate.

Results

Clinical assessment

There was no perioperative mortality in the study group. After a detailed clinical assessment, at which specific leading questions were asked, 106 (84·8 per cent) patients were found to be either symptom free (Visick 1) or to have occasional mild symptoms which did not necessitate any treatment (Visick 2). Of the 19 (15·2 per cent) patients who were dissatisfied with the outcome of surgery (Visick 3 or 4), the reasons were as follows: recurrent reflux, nine; dysphagia, seven; chest pain (post-thoracotomy), two; and gas bloat, one All those with recurrent reflux developed their symptoms within the first year after surgery

24-h pH recordings

One hundred and eight patients had a normal 24-h pH study after operation. Of the remaining 17 patients, a small number (five) has a technically unsatisfactory pH study, mostly owing to probe malposition, electronic malfunction or ingestion of acidic drinks despite instructions to the contrary. All five had a satisfactory symptomatic result and endoscopy showed no evidence of oesophagitis. Twelve patients (9 6 per cent) had demonstrably abnormal reflux – nine of these patients were symptomatic.

Endoscopy

Only eight (6·4 per cent) patients had oesophagitis at endoscopy after operation; all of these patients also had an abnormal pH test and seven were symptomatic. No patient had a hiatus hernia or an oesophageal stricture.

A satisfactory Nissen nipple was found in 115 (92 per cent) patients. Three (2·6 per cent) had an abnormal pH test and two of them also had oesophagitis.

Ten patients had no Nissen nipple suggesting disruption of the fundoplication. Nine (90 per cent) had an abnormal pH test and six of them had oesophagitis The single patient with an absent Nissen nipple and a normal pH study was subsequently demonstrated to have a 'slipped' Nissen. She required reoperation for troublesome dysphagia. Thus there was a very close correlation between the presence of a nipple and control of reflux.

Manometry

The LOS pressure of the group as a whole was significantly increased ($P<0{\cdot}001$) after fundoplication from a median value of 8·4 mmHg (range 0·1–52 mmHg) before operation to 12·7 mmHg (range 3·7–47 mmHg) afterwards. In contrast both the overall length (preoperative: 2 cm median, range 1–6 cm; postoperative. 3 cm median, range 1–6 cm) and the intra-abdominal length of the LOS (preoperative: 1 cm median, range 0–4 cm, postoperative: 2 cm median, range 0–4 cm) were unchanged. We have previously shown that no correlation exists between the mechanical characteristics of the sphincter and reflux control in individual patients. These observations were confirmed in the present study. In 34 patients there was either no change or a decrease in the LOS pressure after operation. Despite this, 31 (91·2 per cent) still had satisfactory reflux control.

In summary, 12 (9·6 per cent) patients had recurrent reflux. In nine (75 per cent) endoscopy had suggested that the Nissen fundoplication had disrupted. Seven had severe symptoms and requested further surgical treatment. At reoperation wrap disruption was confirmed in every case The median time to endoscopic recognition of wrap disruption was 7 months (range 3–10 months). Of the three patients with recurrent reflux and a normal endoscopic appearance, one underwent a repeat endoscopy 24 months after operation at which disruption was demonstrated. All three of these patients had only minor symptoms

Discussion

In the last 20 years or so surgical control of gastro-oesophageal reflux has relied on attempts to boost the action of the lower oesophageal sphincter. The Nissen fundoplication is probably the most widely used procedure at present, but there are many technical variations[13] Studies reporting the results of fundoplication have not been uniformly satisfactory for a number of reasons. Objective methods of assessment before and after operation have not always been used, and even quite recently some have reported results in terms of control of hiatus hernia and not control of gastro-oesophageal reflux. Also the exact operative technique has often not been described. This is an important point as there have been many modifications of the technique originally described by Nissen. Such factors make comparisons between different surgical reports difficult. An additional problem in assessing results is the effect of individual surgical expertise. Some series involve a number of surgeons of variable experience and expertise doing small numbers of operations. Other factors which may make assessment of the results of antireflux surgery less reliable are short duration and adequacy of follow-up.

Our results show that the Nissen fundoplication does achieve a satisfactory outcome in the majority of cases. The major cause of failure is persistent or recurrent gastro-oesophageal reflux, although other problems occur in a significant proportion. Using a strict definition of reflux control, we identified 12 patients (9·6 per cent) in whom the fundoplication had failed. Of this group nine had an abnormal postoperative endoscopic appearance, suggesting fundoplication disruption. Seven underwent reoperation at which time gross disruption of the fundoplication was confirmed. The three patients with recurrent reflux who had a visible Nissen nipple were only mildly symptomatic (Visick 2). It may be that these patients had a wrap which was technically inadequate for some reason but was not completely disrupted.

Brand and colleagues have suggested that the incidence of breakdown of antireflux repairs increases with the passage of time, and that it is 'reasonable to expect only 5–6 years relief from heartburn' after surgery[14]. We think that this conclusion is ill founded. Their study was based on 25 patients who underwent one of three different operations, performed by any one of 14 different surgeons, and of whom only 13 were studied up to 69 months after operation. At least 12 (50 per cent) of their patients had recurrent reflux at 8 months in contrast to only 9·6 per cent of our cases. At 69 months almost 45 per cent of those with satisfactory reflux control initially had developed recurrent reflux. These results strongly question the adequacy of the operations performed in this study. In our larger series of 125 patients with a median follow-up of 52 months, those with recurrent reflux were identified within 10 months of the original Nissen fundoplication.

The mechanism of action of the Nissen fundoplication is still a matter of debate[15]. DeMeester and colleagues[16] have stressed the importance of creating a suitable length of intra-abdominal oesophagus surrounded by the fundoplication which will thus be able to respond positively to increases both in intra-abdominal and intragastric pressure. Maddern and Jamieson[17] have shown that their method of fundoplication superimposes a high resting pressure on the LOS which resists pathological reflux. However several studies have reported that the Nissen fundoplication will control reflux even with an intrathoracic wrap[18]. Thus an intra-abdominal segment of oesophagus is not a prerequisite for success. In addition there may be no increase in either LOS length or resting pressure in successful cases[19]. Liebermann-Meiffert and colleagues have suggested that the alignment of musculature after fundoplication enhances the valvular activity of the LOS[20]. Others have suggested that the fundic musculature may be more responsive to various hormones and that such hormonal activity may be responsible for the beneficial effects[21]. We believe that the mechanism of action is quite simply that of a flap valve which tends to occlude the lower oesophageal lumen as intragastric pressure rises. Such a mechanism would explain the variable results of LOS assessment after operation since an effective flap valve need not exert any resting pressure.

It would appear that recurrent reflux is due to breakdown of the fundal wrap, in spite of careful suture placement and the use of non-absorbable suture material. Some have suggested that this may be precipitated by excessive straining perhaps as early as reversal of anaesthesia[22]. Others suggest that gastric distension in the early postoperative period is an important factor Expert anaesthesia and the appropriate use of nasogastric tube drainage may avoid these problems A different approach has been to try to promote the adherence of the two layers of fundus by serosal electrocoagulation[23] or the use of Teflon® (Du Pont) pledgets[24] A number of authors have emphasized the importance of suturing the oesophagus to the fundic wrap, either at the inferior aspect or along the superior rim[7].

The Nissen fundoplication is a successful surgical solution for refractory gastro-oesophageal reflux disease It is essential for the individual surgeon to audit personal results to ensure adequacy of technique Endoscopic assessment of the fundoplication is a simple and accurate method of detecting fundoplication disruption which is the major cause of recurrent reflux Recognition of disruption as the fundamental problem in failed operations may lead to technical improvements in the future.

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Vomiting after Roux-en-Y biliary diversion: relationship to surgical technique

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Vomiting is a frequent complaint after revisional gastric surgery using a Roux-en-Y biliary diversion. This is believed to be due to gastric stasis or stasis in the jejunal component of the Roux-en-Y. Thirty-three patients, ten with a satisfactory outcome following Roux-en-Y diversion and 23 with an unsatisfactory outcome, were studied using a semisolid, radiolabelled meal and compared with 12 normal subjects. Outcome was assessed by modified Visick grading. Seven patients with an unsatisfactory outcome because of frequent vomiting had gastric stasis and two had delay in emptying of the jejunal component of the Roux-en-Y. Vomiting was more likely in patients with a dependent sump ($P<0.0006$) *and emptying was significantly prolonged where a sump was present* ($P=0.0009$)*. Surgical technique contributed to the dependent sump.*

Keywords: Bilious vomiting, Roux-en-Y diversion

Vomiting frequently follows Roux-en-Y biliary diversion and the incidence varies from 0 to 33 per cent of cases[1]. Proposed mechanisms are anastomotic stenosis, gastric stasis or the 'Roux-en-Y stasis syndrome'. Chronic abdominal pain, postprandial nausea and vomiting are the main complaints in the stasis syndrome and are said to occur because the normal contractile activity of the jejunal component of the Roux-en-Y is lost following vagotomy and anastomosis[2].

We have reviewed the outcome of revisional gastric surgery using the Roux-en-Y diversion in 79 patients[3]. Half the patients had an unsatisfactory result and their main complaints were of upper abdominal pain (46 per cent) and vomiting of food (39 per cent). To determine if persistent symptoms were related to abnormalities of gastric emptying, studies using external imaging of a semisolid, radiolabelled meal were performed in 33 patients with a Roux-en-Y conversion having a satisfactory outcome and an unsatisfactory outcome, and the results compared with 12 normal subjects.

Patients and methods

The indication for the Roux-en-Y diversion in all 33 patients was postoperative reflux gastritis or oesophagitis. Four were women and 29 were men. The mean age was 50 years with a range of 33–78 years, and the interval since Roux-en-Y diversion was a median of 5 years with a range of 0·5–15 years. All the patients were under the care of three surgeons at the Manchester Royal Infirmary. The operations preceding the Roux-en-Y diversion were truncal vagotomy and drainage in 14, cholecystectomy in three, partial gastrectomy in two, truncal vagotomy and drainage with cholecystectomy in five, truncal vagotomy and drainage with resection in four, partial gastrectomy with cholecystectomy in four and hiatal hernia repair in one.

The Roux-en-Y diversion was performed after Billroth II partial gastrectomy by dividing the afferent loop and anastomosing this a median of 45 cm down the small bowel. Where the stomach was intact antrectomy was performed routinely with the diversion. Two surgeons performed a 50 per cent resection and the other an anatomical antrectomy. For the gastrojejunal anastomosis one surgeon used an isoperistaltic anastomosis and the other two an antiperistaltic anastomosis. Truncal vagotomy was not performed routinely but was added in three patients. Twenty-six of the patients studied had a truncal vagotomy performed before or with the diversion.

Four groups were studied: 12 normal subjects, ten patients with a satisfactory result after Roux-en-Y diversion, 12 patients with an unsatisfactory result who vomited frequently (more than once per week), and 11 patients with an unsatisfactory result in whom pain was the main complaint (four complained of infrequent vomiting, less than once per week). Vomiting was established in all these patients within 3 months of operation. All the patients with an unsatisfactory result were examined by gastroscopy and/or barium meal and none had a recurrent ulcer, anastomotic stenosis or bezoar.

Methods

Gastric emptying was studied using 160 ml of porridge labelled with 12 MBq of ^{99m}Tc tin colloid. The patient was seated in front of a γ-camera (International General Electric, St Albans, UK, Maxicamera 400 A/T fitted with a low energy collimator). A dynamic acquisition of 1-min frames was started as soon as the patient began to eat. After 35 min the dynamic acquisition was stopped and intermittent 2-min static images were obtained every 15–30 min up to a maximum of 2 h. No correction was made for tissue attenuation as a small volume, semisolid meal[4,5] was used and any error was negligible as the distal stomach had been excised. Data were analysed on a MDS (Medical Data Systems, Ann Arbor, Michigan, USA) A[3] computer. A region of interest was drawn around the gastric remnant and if there was evidence of hold-up on the dynamic images a region was drawn around the jejunal component of the Roux-en-Y. Results were obtained as curves of the percentage of the ingested activity in the regions as a function of time. The rate of emptying was quantified from the gastric curves by the length of lag phase and the half emptying time ($T_{1/2}$) of the emptying phase. The $T_{1/2}$ was calculated from the best linear or exponential fit to the emptying phase. Gastric stasis was defined as a $T_{1/2}$ or lag phase greater than the maximum value obtained in the ten Roux-en-Y patients with a satisfactory clinical result and the 12 volunteers.

Results

In normal subjects the lag phase was short because of the semisolid nature of the meal and emptying was usually linear after this. In contrast, the typical pattern of emptying observed in patients with Roux-en-Y was best described by a simple decreasing exponential. Only four patients with Roux-en-Y had a lag phase and all were within the normal range (0–23 min). The values of $T_{1/2}$ for the emptying phase when related to symptoms are shown in *Figure 1*. Seven patients who vomited frequently had delayed emptying and in three this was preceded by initially rapid emptying. Two other patients who vomited frequently with gastric $T_{1/2}$ within the normal range had hold-up in the jejunal component of the Roux-en-Y for 17 and 32 min, respectively. Neither of these patients had evidence on barium follow through of obstruction and on re-exploration in one no mechanical abnormality was found. These patients also had normal manometric findings in the jejunal component of the

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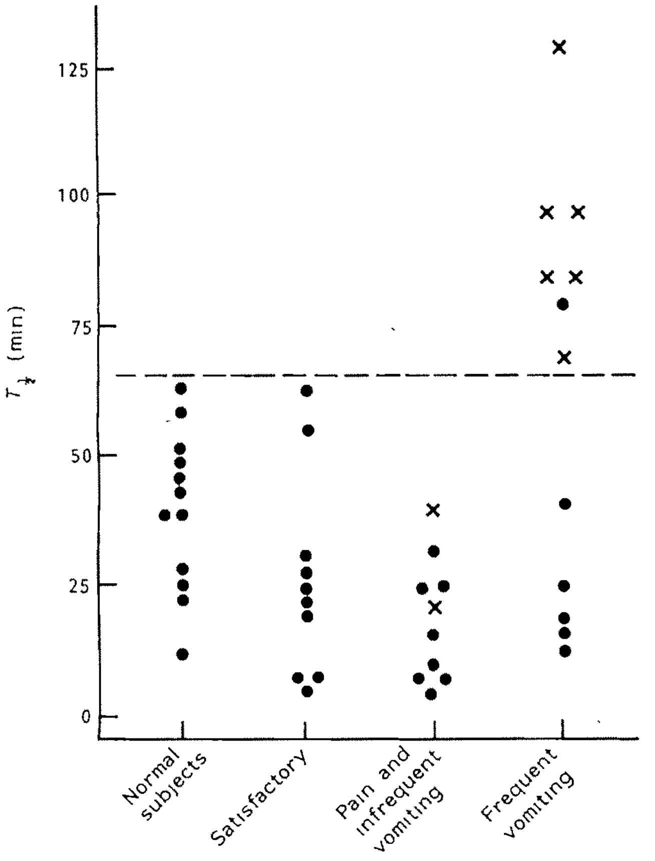

Figure 1 *Half emptying time of the emptying phase* ($T_{1/2}$) *in normal subjects* (n = *12*) *related to outcome and symptons in Roux-en-Y patients* (n = *33*) X, *dependent sump*

Roux-en-Y. Pain with or without infrequent vomiting was not related to a delay in emptying.

Review of the images of the radionuclide emptying tests and the barium meals showed that eight patients had a dependent portion of the gastric remnant below the level of the gastrojejunal anastomosis, creating a sump (*Figure 2*). Vomiting was more common and tended to be more severe in those patients with a dependent sump; all eight patients with a sump vomited compared with eight of 25 patients without a sump ($P < 0{\cdot}0009$, Fisher's exact test). The $T_{1/2}$ was significantly prolonged in patients with a dependent sump; median of 83 min, range 24–129 min for those with a sump compared with a median of 20 min, range 4–78 min for those without ($P = 0{\cdot}0006$, Mann–Whitney U test). Six of the seven patients with gastric stasis had a dependent sump.

Discussion

The procedure we performed as a Roux-en-Y diversion was modified from that originally described by Roux[6]. He described a retrocolic, posterior gastroenterostomy with Y reconstruction mainly in the treatment of gastric carcinoma. Because of the risk of stomal ulceration, Roux-en-Y diversion now includes antrectomy with or without truncal vagotomy.

It is unclear whether persistent vomiting is due to gastric stasis or to stasis within the jejunal component of the Roux-en-Y. It has been suggested that vomiting is related to the length of the jejunal component[1] but we did not confirm this[3]. There are manometric abnormalities in the jejunal component of the Roux-en-Y, and stasis has also been demonstrated on radionuclide emptying tests[2,7]. Both of these studies were in small, selected groups but similar abnormalities were not found in a study[8] involving a larger number of patients where no stasis was seen and the clinical relevance of the manometric abnormalities described was questioned

Our results show that gastric stasis is the main cause of frequent vomiting and that Roux-en-Y stasis is less common. Seven of the patients we studied had prolonged emptying rates indicating gastric stasis and two had stasis in the jejunal component of the Roux-en-Y. Two factors are claimed to be responsible for stasis, loss of the distal gastric pump and alteration of motility by vagotomy[9,10]. Antrectomy which was performed routinely removed part of the distal pump. Truncal vagotomy, which had been carried out in 26 of the 33 patients, alters fundic pressure[11] and may alter small bowel contractility[12]. Each of these could result in stasis and gravity may be the only factor determining emptying.

Although alluded to in other studies[8,13], our results confirm that if, in addition to the above factors, a dependent sump was present, vomiting was more likely. In our patients surgical technique contributed to the sump and we propose that the high incidence of food vomiting (39 per cent compared with that reported by Donovan *et al.* (5 per cent)[8] is due to differences in surgical technique. Our experience suggests that if patients have had a truncal vagotomy the gastrojejunal anastomosis should be placed antiperistaltically (*Figure 3*) and antrectomy

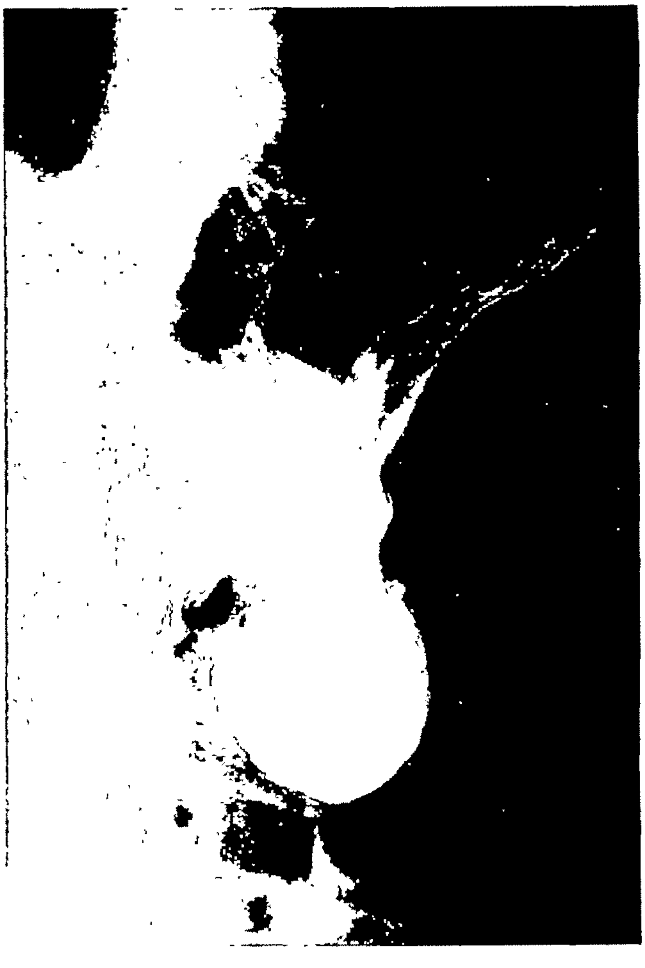

Figure 2 *Barium meal showing a dependent sump in a Roux-en-Y patient*

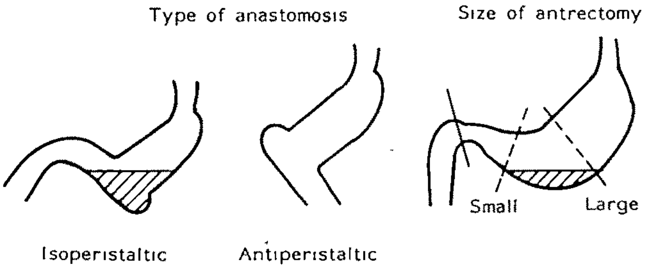

Figure 3 *Diagram of surgical factors contributing to a dependent sump*

should include sufficient greater curvature so that a dependent sump is avoided. It may be that a subtotal gastrectomy is the only way to achieve this[14] as the atonic remnant may dilate following diversion. We have performed subtotal gastrectomy in seven patients with frequent vomiting but long-term results are not available although others report a satisfactory result[15].

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Outcome of revisional gastric surgery using a Roux-en-Y biliary diversion

One hundred and seven patients with postoperative reflux gastritis treated by Roux-en-Y biliary diversion were reviewed. Three patients died in the postoperative period, and 16 others have since died; cardiorespiratory disease was the most frequent cause of death. Seventy-nine patients were interviewed at a median of 5·5 years (range 0·5–26 years) following Roux-en-Y diversion. At review, a satisfactory result by modified Visick grading was present in 47 per cent of patients. Bilious vomiting ($P<0{\cdot}001$), *food vomiting* ($P<0{\cdot}01$), *the severity of upper abdominal pain* ($P<0{\cdot}001$) *and heartburn* ($P<0{\cdot}025$) *were significantly improved by Roux-en-Y diversion. Weight, haemoglobin levels and employment status were not significantly altered by the procedure. Outcome was related to the surgery preceding Roux-en-Y diversion with significantly better results after partial gastrectomy compared with truncal vagotomy and drainage* ($P<0{\cdot}01$), *cholecystectomy* ($P<0{\cdot}05$), *or combinations of these procedures* ($P<0{\cdot}01$). *Outcome was not predicted by sex, preoperative symptoms, smoking status, consultant surgeon, length of Roux-en-Y or ^{99}Tc-Sn-2,6-diethylacetanilidoiminodiacetate (HIDA) scanning results.*

Keywords: Bilious vomiting, Roux-en-Y diversion, HIDA

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The Roux-en-Y diversion is the most commonly used reconstruction for bilious vomiting following previous surgery. Epigastric pain and heartburn are often associated and, together with evidence of gastritis, the syndrome has been referred to as 'reflux gastritis' or 'alkaline reflux gastritis'. It is not known whether refluxing duodenal contents are responsible for persistent symptoms[1]: Earlier reports[2,3] claimed good or excellent results in over 65 per cent of cases treated with a Roux-en-Y diversion but recent studies have claimed that only bilious vomiting[4–6] is resolved and that the procedure is ulcerogenic and invariably induces malabsorption[7]. Vomiting of food is a frequent complication following diversion and the reported incidence varies from 0 to 33 per cent of cases[8].

We reviewed the outcome of revisional gastric surgery using the Roux-en-Y diversion in patients operated on by three consultant surgeons at the Manchester Royal Infirmary. The Roux-en-Y diversion has been the favoured technique of reconstruction of H B T. for over 26 years and has been used by the other two surgeons for 10 years.

Patients and methods

Of 107 patients reviewed, 80 were traced, 19 patients had died and 8 patients could not be traced. The cause of death, post-mortem findings and any further operative intervention that had been required elsewhere were ascertained for all 19 patients who died

Patients traced were invited to attend for interview or visited at home. All interviews were undertaken by G H.F and each patient was given a modified Visick grading[9] based on the symptoms at the time of interview grade 1, an excellent result without symptoms; grade 2, a good result with mild symptoms only; grade 3, a satisfactory result, with moderate symptoms, not controlled by diet, causing some discomfort, but the patient is satisfied with the result; and grade 4, an unsatisfactory result. Patients were asked to compare pre- and postoperative symptoms and whether they felt improved, unchanged or worse as a result of the Roux-en-Y Employment status before and after operation was noted and each patient was scored on the Karnofsky scale of performance status Weight and height were measured and weight was graded as low, acceptable or obese[10]. Blood was taken for full blood count, vitamin B_{12}, serum and red blood cell folate, serum iron, total iron binding capacity and albumin Haemoglobin, albumin and weight were compared with preoperative values Vitamin D levels were measured in the latter part of the study All patients with an unsatisfactory result had either a gastroscopy or barium meal.

Statistical analysis

For analysis patients with a Visick 1, 2 and 3 grade at interview were grouped together and compared with Visick grade 4. Outcome defined by these two groups as either satisfactory or unsatisfactory was related to: age using Student's t test, sex, preoperative symptoms, preceding surgery, consultant surgeon and smoking status using the χ^2 test, length of symptoms and the length of the Roux-en-Y by the Mann–Whitney U test; and ^{99}Tc-Sn-2,6-di-ethylacetanilidoiminodiacetate (HIDA) scan result using Fisher's exact test. Changes in symptoms, weight and employment status before and after surgery were analysed using McNemar's test for the significance of change. Pre- and postoperative haemoglobin and albumin levels were compared using the paired t test The Mann–Whitney U test was used to compare postoperative symptoms with the length of the jejunal component of the Roux-en-Y The level for significance was $P<0{\cdot}05$.

Patients reviewed

Seventy-two patients were men and 35 were women. The average age at operation was 46 years (range 23–75 years). The indications for Roux-en-Y were bilious vomiting in 92 per cent of patients, upper abdominal pain in 82 per cent and heartburn in 25 per cent. In addition, weight loss was present in 64 per cent of patients and anaemia in 13 per cent Symptoms were present before Roux-en-Y for a median of 4 years (range 1–30 years) At the time of operation 40 of the patients had other disabling medical conditions including chronic obstructive airways disease (seven cases), arthritis (nine cases) and chronic pancreatitis (eight cases); 66 per cent of patients were smokers.

Previous surgery

The operations undertaken before the Roux-en-Y diversion are listed in *Table 1* In 54 per cent of patients the initial surgery had been performed at another hospital. Although there was often one operation from which the patient dated the onset of symptoms other previous surgery may have contributed. Truncal vagotomy had been performed in 63 per cent of patients before revision. The majority of partial gastrectomies were Billroth II reconstructions and none was performed for malignancy. Cholecystectomy was the only preceding operation in

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Table 1 *Surgery preceding Roux-en-Y in 107 patients*

Type of surgery	No.
Truncal vagotomy + drainage	33
Partial gastrectomy	21
Cholecystectomy	10
Truncal vagotomy + drainage + cholecystectomy	18
Truncal vagotomy + drainage with subsequent partial gastrectomy	14
Partial gastrectomy + cholecystectomy	7
Other combinations of procedures	4

12 patients had a hiatus hernia repair in addition to the surgery listed

9 per cent of patients but in a further 25 per cent cholecystectomy had been carried out in addition to other procedures. Previous attempts to treat reflux had been undertaken in eight patients (two reversed loops, two reconstructions of pylorus, three enteroanastomoses and one closure of gastroenterostomy). The interval between initial surgery and Roux-en-Y was a median of 6 years (range 1–38 years).

Preoperative assessment

This altered over the years reflecting changing trends in management. Barium meal and gastroscopy were undertaken routinely. In 8 per cent of patients the endoscopy was normal. Patients with recurrent ulcers were not included in this review. In the past eight years HIDA scanning was used to establish the presence of duodenogastric reflux. The test was performed on 25 of the patients who were traced, but in eight no reflux was demonstrated. Roux-en-Y diversion was still performed because of the severity of symptoms.

Roux-en-Y diversion

Operation was undertaken by a consultant surgeon in all but 11 instances when it was undertaken by the senior registrar. After Billroth II gastrectomy the Roux-en-Y diversion was performed by division of the afferent loop and reanastomosis further down the small bowel. In patients with an intact stomach technique differed between surgeons. Roux[11] originally described a retrocolic, posterior gastroenterostomy in the treatment of obstructing cancers, but his technique has been modified to decrease the risk of stomal ulceration. There is no common agreement on size of antrectomy, anastomotic technique or the need for truncal vagotomy[12]. The median length of Roux-en-Y performed in this study was 45 cm; one surgeon used a 25–35 cm loop and the others a 40–60 cm loop. One surgeon used an isoperistaltic technique for the gastrojejunal anastomosis and the other two an antiperistaltic technique. One performed anatomical antrectomy and the other two a 50 per cent resection. Truncal vagotomy was not performed routinely but was added at the time of Roux-en-Y diversion in 13 patients. Nissen fundoplication was performed in addition in three patients.

Results

Deaths

The causes of death since Roux-en-Y diversion and the age at death are shown in *Table 2*. There were three postoperative deaths from sepsis because of anastomotic leaks. The main cause of death was cardiorespiratory disease. Death occurred a median of 6 years (range 1–21 years) after diversion. In only one case was malnutrition obviously related to death.

Patients interviewed

Eighty patients (91 per cent) available for follow-up were traced. One patient was misdiagnosed and required coeliac artery release before his pain was cured and he was excluded from analysis, leaving 79 patients. Two patients had further gastric surgery elsewhere and details were obtained from their respective consultants. The interval between Roux-en-Y diversion and interview was a median of 5·5 years (range 0·5–26 years).

The Visick grading at interview is shown in *Table 3*. Fifty-three per cent of patients had an unsatisfactory result. Outcome related to previous surgery is listed in *Table 4*. Outcome was significantly better where the surgery preceding Roux-en-Y diversion was a partial gastrectomy compared with truncal vagotomy and drainage ($\chi^2 = 7{\cdot}64$, $P < 0{\cdot}01$), cholecystectomy ($\chi^2 = 4{\cdot}77$, $P < 0{\cdot}05$), truncal vagotomy and drainage with cholecystectomy ($\chi^2 = 12{\cdot}82$, $P < 0{\cdot}01$) or resection combined with either of these procedures ($\chi^2 = 7{\cdot}61$, $P < 0{\cdot}01$). Outcome was not related to age, sex, preoperative symptoms, smoking status, length of preoperative symptoms, consultant surgeon, length of Roux-en-Y or operative histology.

Further surgery was required in the interval after diversion in 15 patients. Only one patient required re-vagotomy for stomal ulcer. In one patient malignant change was found within the gastric remnant 1 year after Roux-en-Y conversion and he required total gastrectomy. Two patients were treated elsewhere: in one the Roux-en-Y was dismantled and in the other modified. Cholecystectomy has been performed subsequently in six patients for symptomatic gallstones. Three patients had laparotomies for adhesive obstruction. One patient had a Nissen fundoplication revised and one had an Angelchik prosthesis inserted. Of these 15 patients only the three who required cholecystectomy were satisfactory at interview.

The Visick grading at interview related to the presence or absence of duodenogastric reflux on HIDA scanning is shown in *Table 5*. In patients in whom reflux was demonstrated this did not invariably predict a successful outcome. The outcome after Roux-en-Y diversion for the 17 patients with reflux on HIDA scanning was not significantly different from the eight without reflux. Thirteen patients had repeat scans following operation and in only one was reflux still demonstrated.

By their own assessment 56 patients felt some improvement, 13 were unchanged and ten were worse following Roux-en-Y.

Table 2 *Causes of death in 19 patients after Roux-en-Y surgery*

Cause of death	No. of deaths (age in years)
Postoperative leak with septicaemia	3 (39, 56, 71)
Cardiorespiratory	7 (36, 52, 53, 67, 68, 71, 81)
Malignancy	5 (43, 67, 73, 80, 82)
Pancreatitis	2 (39, 44)
Septicaemia with liver abscess	1 (73)
Suicide	1 (29)

Table 3 *Visick grade in the 79 patients reviewed*

Visick grade	No. of patients (%)
1 Excellent	4 (5)
2 Good	18 (23)
3 Satisfactory	15 (19)
4 Unsatisfactory	42 (53)

Table 4 *Visick grade related to surgery preceding Roux-en-Y in the 79 patients reviewed*

	Visick grade	
Previous operations	1, 2 or 3	4
Partial gastrectomy	11	1
Truncal vagotomy + drainage	11	14
Cholecystectomy	5	5
Truncal vagotomy + drainage + cholecystectomy	3	11
Partial gastrectomy + vagotomy or cholecystectomy	7	11

Multiple comparison between groups χ^2 13·89, $P < 0{\cdot}01$

Table 5 *Result of preoperative HIDA scan related to Visick grade at review in 25 patients*

Visick grade	Reflux present	No reflux demonstrated
1, 2 or 3	7	3
4	10	5

Comparison between all four groups. $P = 0{\cdot}6$ (not significant) using Fisher's exact test

Table 6 *Changes in symptoms, weight and employment status before and after Roux-en-Y surgery in 79 patients*

	No of patients		
	Before surgery	After surgery	
Vomiting			
bile	68	4	$P<0{\cdot}001$
food	49	31	$P<0{\cdot}01$
Severe or moderate upper abdominal pain	55	37	$P<0{\cdot}001$
Severe or moderate heartburn	21	10	$P<0{\cdot}025$
Dumping (systemic symptoms)	8	9	n s.
Loose stools >3 per day	20	26	n s.
Weight lower than acceptable range	27	19	n.s
Employment status			
Invalid	37	34	n s.
Employable	30	33	n s
Retired	12	12	

n s., Not significant *P* values obtained using McNemar's test for the significance of change

Table 7 *Karnofsky scores at review in 79 patients*

Score	No. of patients
10 Normal, no complaints	4
9 Able to carry on normal activity, minor symptoms	25
8 Normal activity with effort, some symptoms	17
7 Cares for self, unable to carry on normal activity	20
6 Requires occasional assistance and frequent medical care	8
5 Requires considerable assistance and frequent medical care	5

The changes in specific symptoms, weight and employment status before and after surgery are shown in *Table 6*. There were significant improvements for bilious vomiting, food vomiting, the severity of upper abdominal pain and heartburn but only bilious vomiting was consistently improved. Persistent pain and vomiting of food were the main reasons for an unsatisfactory result following Roux-en-Y. Neither symptom was related to the length of the Roux-en-Y (pain, $P=0{\cdot}95$; vomiting, $P=0{\cdot}82$; Mann–Whitney *U* test).

There was no statistically significant change in weight (mean(s.d.) preoperative weight of 63(13) kg compared with postoperative weight of 64(13) kg; paired *t* test). Five patients lost over 5 kg following diversion, four had gastric stasis and the fifth required total gastrectomy Ten patients (13 per cent) were anaemic at the time of review. Overall there was no statistically significant change in haemoglobin levels (preoperative mean(s.d.) 13·7(2·2) g/100 ml compared with postoperative 13 9(1·9) g/100 ml, paired *t* test). Five patients had required transfusion for anaemia since Roux-en-Y diversion Six patients were on iron supplements, a further three patients had low serum iron levels and the total iron binding capacity was raised in 15 patients. Three patients were on vitamin B_{12} replacement and two others were found to be deficient in vitamin B_{12}. No patient had folate deficiency There was a significant improvement in albumin levels (from a preoperative mean(s d.) level of 39·8(4 6) g/l to postoperative 43(5·3) g/l; $P=0{\cdot}0004$, paired *t* test) The levels of 25-hydroxy derivatives of vitamins D_2 and D_3 were measured in 25 patients after diversion Only two patients showed an absolute deficiency of vitamin D but neither was symptomatic. None of the patients in whom vitamin D levels were assessed had raised alkaline phosphatase, but one had a low corrected calcium and one a low phosphate

The Karnofsky scores at review are listed in *Table 7*. Thirteen patients had a score lower than 7 and they could be considered 'gastric cripples' but other medical problems often contributed to their disability. For instance, three had strokes during the follow-up period.

Discussion

The present series is the largest reported in the UK on the outcome of Roux-en-Y diversion. All the patients in this review were interviewed by one independent observer. Seventy-nine patients were interviewed and 47 per cent had a satisfactory result which is similar to recent reports[4,5].

The main indication for the Roux-en-Y diversion was bilious vomiting. Gastritis or oesophagitis at endoscopy was not considered essential to recommending revision although most patients had one or both of these abnormalities. Bilious vomiting was frequently associated with upper abdominal pain and heartburn and all of these symptoms were significantly improved by diversion, though only bilious vomiting showed a consistent improvement. Of the 79 patients reviewed, four still complained of bilious vomiting but 37 had moderate or severe upper abdominal pain and 31 complained of vomiting of food. Pain may persist because of co-existing chronic pancreatitis, irritable bowel disease or stasis in the gastric remnant. In a few patients psychological causes are suspected. Pain is the most difficult single symptom to treat and we would not advise Roux-en-Y diversion where this was the only complaint.

Duodenogastric reflux can cause bilious vomiting after partial gastrectomy[13] but similar studies have not been performed after truncal vagotomy and drainage. Our results confirm that the Roux-en-Y diversion is an adequate method of treating bilious vomiting after partial gastrectomy but the results were disappointing after truncal vagotomy and drainage. The mechanism of bilious vomiting following truncal vagotomy and drainage is not understood and often these patients complain of vomiting of food as well. Bilious vomiting may be secondary to changes in gastric motility in these patients rather than a primary irritant effect of refluxing duodenal contents on the gastric mucosa. In one study[14] indirect evidence of altered gastric motility was demonstrated before the diversion. On a barium burger meal several patients had delayed gastric emptying and these patients had a worse outcome than those with normal emptying. Using radionuclide emptying tests several studies have failed to demonstrate a clear association between rate of emptying and symptoms before diversion[15,6]. In our preoperative assessment of patients with bilious vomiting after truncal vagotomy and drainage using compressed radionuclide image analysis[16] we have found that two-thirds of patients have gross abnormalities of gastric motility.

Duodenogastric reflux is increased after cholecystectomy[17] and is believed to be responsible for bilious vomiting, but only five of the ten patients in whom cholecystectomy was the sole previous operation obtained a satisfactory result. One reason for this may be the addition of a truncal vagotomy at the time of diversion as this places these patients at the same risk of stasis as those with a vagotomy before diversion. Three of these patients with an unsatisfactory outcome, all of whom had vagotomy performed at the time of diversion, had gastric stasis Pylorus-preserving procedures such as described by de Meester *et al*[18] may be better in this type of patient.

There are claims for a variety of methods in predicting the outcome of revisional surgery[19,20]. In this review, only the type of surgery preceding revision was found to be predictive. The presence or absence of duodenogastric reflux on HIDA scanning did not relate to outcome and this casts further doubt on reflux as a primary cause of bilious vomiting, particularly in patients who have had truncal vagotomy and drainage.

The consequences of Roux-en-Y diversion cannot be ignored. The procedure is associated with significant morbidity and mortality rates, a point emphasized previously[7]. Nevertheless, we would disagree that the Roux-en-Y diversion combined with antrectomy and vagotomy is ulcerogenic or that the procedure invariably results in malabsorption. Only one patient developed a stomal ulcer and there were no cases of perforation or bleeding. Other studies claim a similar low incidence[3,4,21]. At interview 14 per cent of patients were anaemic and 27 per cent had a low weight but neither haemoglobin levels nor weight were significantly altered by Roux-en-Y diversion. Albumin levels improved significantly after surgery. The nutritional problems present were usually related to previous surgery and lifestyle rather than the diversion and the incidence cited in this review was little different from that reported following Billroth II gastrectomy[22]. Similarly, the causes of death following Roux-en-Y diversion were little different from those reported following peptic ulcer surgery[22,23]. In both there is an increased risk of premature death which is often associated with smoking-related disease.

With an unsatisfactory outcome in so many patients the continued use of the Roux-en-Y diversion for symptoms of postoperative reflux gastritis may be questioned. Nevertheless, almost one half of the patients achieved a satisfactory result which, in the absence of any other effective therapy for these beleagured patients, would justify the use of the procedure in the minds of many. The indications for diversion continue to be based on symptoms and by the exclusion of other pathology. Medical treatment is rarely of benefit although this should be used before considering revision. We have not found the new prokinetic agent, cisapride, of any benefit in treating ten patients with bilious vomiting. When revisional surgery is considered, the patient should be aware that the result cannot be predicted and that palliation is often all that is achieved.

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First rib resection for vascular complications of thoracic outlet syndrome

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The surgical approach to vascular complications of the thoracic outlet syndrome remains controversial. When present, removal of a cervical rib alone has produced disappointing results. Our experience of 29 consecutive first rib excisions over a 5-year period is presented. Of 20 cases with uncomplicated subclavian artery compression 19 were cured, and of six cases with aneurysm or thrombosis five were improved. Of 12 cases with neurological symptoms nine were cured and two were improved. It is suggested that first rib excision is the essential primary treatment for patients with arterial symptoms due to thoracic outlet syndrome.

Keywords: Thoracic outlet syndrome, first rib

The diagnosis and management of the thoracic outlet syndrome continues to be one of the most difficult problems facing the vascular surgeon. The symptom complex arises from neurological or vascular compression lateral to the thoracic inlet itself, involving the subclavian vessels or the lowest trunk of the brachial plexus.

The primary mechanism is either costoclavicular compression between the clavicle and the first rib, or costoscalene compression between the surface of scalenus anterior and a cervical or first rib. Both of these primary factors may be complicated by secondary mechanisms such as fibrous bands between a vestigial cervical rib and the scalene tubercle, or anatomical variations of the scalene musculature[1].

Resection of the first rib, originally proposed by Bramwell in 1903[2], is an attractive approach, because the first rib acts as the fixed point about which thoracic outlet compression can occur. At operation after removal of the rib the neurovascular bundle can be seen to fall away inferiorly, free of restriction.

The results of first rib resection in a series of 20 patients with 29 affected arms are presented.

Patients and methods

Consecutive patients referred to a single surgeon over a 5-year period ending in 1988 were studied. Clinical details are outlined in *Table 1* and presenting symptoms and their duration are summarized in *Figure 1*.

Vascular involvement was characterized by symptoms of diffuse brachial pain on exercise, particularly with the arm elevated, which did not follow a neurological distribution. Diagnosis was based primarily on the history and clinical assessment. It is a particular feature of thoracic outlet syndrome that there remains a lack of positive investigations to confirm all but the most clear cases of vascular compression. Disappearance of the pulse during various manoeuvres is a common finding in normal individuals. The Roos Test[3], in which the shoulders are braced backwards and the elevated hands are repeatedly clenched to reproduce the symptoms, is very convincing when positive, as it was in 95 per cent of this series. However, all those familiar with thoracic outlet syndrome are conscious of the unsatisfactory diagnostic situation, which is often only resolved by the dramatic relief of symptoms after operation.

Five patients thought to have neurological involvement all had normal electromyograms before referral. Arteriography was performed in all but two patients, and identified five aneurysms and three cases of subclavian artery thrombosis. In 20 limbs, arteriography revealed no evidence of structural abnormality in the subclavian artery. We have found that oblique arteriographic views can demonstrate subclavian compression which may not be evident on the anteroposterior projection.

Latterly, duplex ultrasonography has been introduced. Turbulence and stenosis in the subclavian artery has been found in six patients who were confirmed to have arterial involvement at operation,and postoperative examinations have all been normal. Duplex has an increasingly important place in the assessment of patients with vascular symptoms due to subclavian compression.

Management policy

The transaxillary approach alone was employed in patients who were judged to have uncomplicated neurovascular compression. Early in the series the supraclavicular approach was selected if reconstruction of the subclavian artery was anticipated, as it gives improved exposure for proximal control. However, following this early experience, and that of others[4], a two stage procedure is now performed. This is described below.

Operative technique

The patient is placed in the half lateral position and the forearm is towelled separately. A skilled assistant is positioned at the head of the table (a stool is of value), holding the flexed elbow over his forearm. Vertical traction opens the axilla and is of prime importance in achieving adequate exposure. It is essential that the arm is released from traction at intervals to avoid ischaemia.

A transverse incision is made at the level of the inferior axillary

Table 1 *Clinical details of 20 patients*

Number of affected limbs	29
Female:male ratio	15:5
Median age in years (range)	36 (19-55)
Median duration of symptoms in months (range)	21 (1-60)
Number of cervical ribs	11

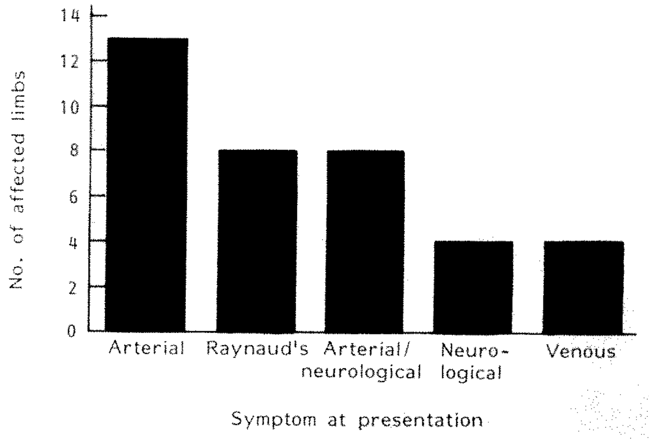

Figure 1 *Symptoms at initial presentation*

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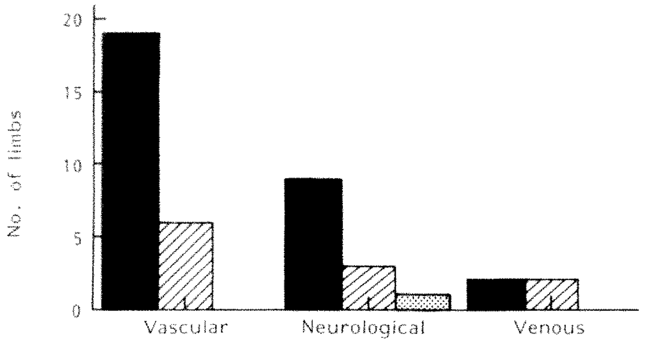

Figure 2 *Clinical outcome following surgery.* ■, complete relief; ▨, *partial relief; and* ▩, *no relief*

hair line. The dissection is deepened directly on to the chest wall to keep below the axillary contents. The intercostobrachial nerve is identified and allowed to fall laterally. Dissection then follows the axillary artery proximally until the scalene groove of the first rib is encountered. Division of the superior intercostal artery frees the neurovascular bundle, which can be gently retracted upwards. The scalenus anterior insertion is divided close to the scalene tubercle, and a portion of this muscle is resected along with any anomalous muscle slips which may be encountered attached to the rib. This ensures that the periosteum is removed along with the rib. This is essential to prevent regrowth of the bone. Sibson's fascia, overlying the apex of the pleura, is reflected from the inferomedial aspect of the first rib by gentle finger dissection. A deep narrow retractor is useful to protect the neurovascular bundle when the rib is cut. Angled shears specifically designed for first rib resection are desirable to allow division of the rib as posteriorly as possible, and as near the costoclavicular joint as possible. Residual or sharp bone fragments are smoothed with bone nibblers.

If the artery is to be reconstructed, the transaxillary resection is completed and the wound closed. The patient is moved to the supine position, redraped, and the reconstruction performed via a supraclavicular incision. The new position allows the shoulder to fall back and greatly improves proximal access. If an obvious pneumothorax is encountered, an intercostal drain is inserted and the wound closed in two layers. An erect radiograph of the chest is performed in the recovery room and will identify any pneumothorax not previously noted. Wound drains are not routinely used as they may predispose to infection[1] and possibly lymphatic fistula.

Follow-up

After operation patients were assessed in the clinic. Later results have been compiled from interviews and clinical examination between 4 and 46 months after surgery (median 26 months). The results of operation were found to lie in three distinct categories: complete relief, partial relief, and no relief. No further grading was considered appropriate. The only late 'surgical' problem was a keloid scar in the axilla of a 23-year-old Asian patient.

Results

Twenty transaxillary resections were performed, of which three included resection of both cervical and first ribs. A combined approach was necessary in four of the nine supraclavicular operations performed.

One patient sustained peroperative damage to the T1 nerve root, and has a residual neuropraxia. This occurred early in the series, before the use of angled rib cutters. Intercostal drainage was required for the treatment of apical pneumothoraces in two supraclavicular and two transaxillary resections. There has been no evidence of phrenic nerve palsy as judged by raised hemidiaphragm on postoperative radiographs. No wound infections have been seen.

Seventy-six per cent of patients with vascular symptoms, and 75 per cent with neurological symptoms reported complete relief following surgery (*Figure 2*). There was no difference in outcome between the two surgical approaches. Two patients with arm swelling due to venous involvement were cured, and two were helped. In view of the small numbers involved it is not proposed to discuss venous obstruction in this paper. The results in arterial and neurological involvement compare favourably with published series, and it is significant that five out of six patients with only partial relief of their symptoms presented with complicated subclavian compression.

Figure 2 illustrates more symptoms that were apparent at initial presentation. This discrepancy is due to longstanding arterial insufficienty in patients who actually presented with other symptoms. Successful decompression can lead to an improvement in exercise tolerance in the elevated limb, and it appears that some patients are not aware of this limitation until the operation affords relief. We have also noted this effect following carotid endarterectomy, where several patients have reported an improvement in memory and concentration which was unexpected and unrelated to their presenting symptoms.

Three arterial cases are worthy of individual consideration. A lorry driver presenting with irreversible ischaemia due to extensive emboli from the subclavian artery unfortunately required amputation of his right forearm. His symptoms were of 2 weeks duration.

A 46-year-old female developed painful hands following nasal septoplasty at another hospital. During the operation her neck had been extended with the assistance of a sandbag placed between her shoulders. At presentation 48 h later she was found to have multiple bilateral digital emboli and gangrene of several finger tips. She had no previous symptoms. Despite urgent operation she has been left with tissue loss and disabling causalgia.

An interesting observation was noted in the case of a 43-year-old nurse who was referred with a clearly visible subclavian aneurysm distal to stenosis due to a cervical rib (*Figure 3*). The external diameter of the aneurysm was determined with ultrasonography and found to be 3·5 cm. At operation both the first and cervical ribs were resected through the axilla to free the artery. As it was proposed to insert a vascular graft, the artery was exposed through the neck, and was found to have returned to its normal diameter. This appeared to be an example of a 'haemodynamic aneurysm', where the dilatation occurs in a normal artery between the proximal stenosis and the distal peripheral resistance. After careful inspection the artery was left untouched, with no sequelae.

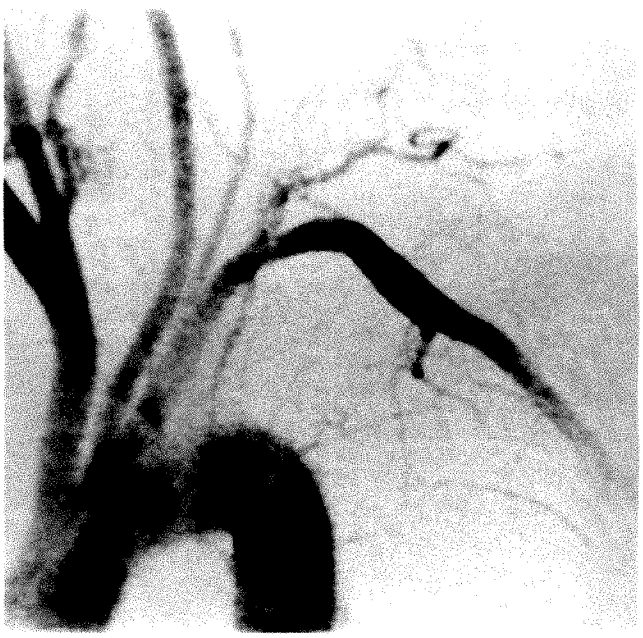

Figure 3 *Digital subtraction angiogram showing a dilated subclavian artery, representing a 'haemodynamic' aneurysm*

Discussion

The Australian surgeon, Thomas Murphy, was the first to remove a normal first rib for plexus compression, in 1910[5]. The posterior parascapular approach of Clagget[6] was followed by the first description of the transaxillary approach, by Roos, in 1966[7]. Roos has reported excellent results. Of 1315 patients treated by complete outlet decompression 1210 (92 per cent) have had 'substantial long term relief', with a reoperation rate of 2·2 per cent[1].

However, most reports concentrate on the results in terms of neurological symptoms. Scher *et al.*[8] divided arterial compression due to cervical rib into three stages, depending on the degree of intimal damage, and recommended rib resection in all cases. A recent series has emphasized that patients with arterial involvement are not cured by cervical rib excision alone[9], and we must agree with Cormier *et al.*[10] that, whatever else is done, removal of the first rib is of vital importance. Furthermore, several authorities[4,11], have described their progression through various limited soft tissue operations to transaxillary first rib resection, with whatever other procedures are necessary being performed through a separate supraclavicular incision.

As regards follow-up, the mean time interval for recurrent symptoms in a recent review of 60 cases was found to be 4 months, with 63 per cent recurring within 6 months[12]. The limitations of a retrospective analysis are appreciated, even when supplemented by patient interviews and objective assessment of the results. Nevertheless, a prospective study would be difficult in view of the comparatively small number of cases seen by most surgeons.

Five of the six patients with only partial relief of their arterial symptoms presented with complications (two subclavian thromboses and three aneurysms) and the risk of losing the limb because of arterial thrombosis is illustrated by the cases described above. The preponderance of arterial cases reported in this series reflects referral to a specialist unit, but this experience emphasizes that brachial ischaemia or unilateral Raynaud's phenomenon should be investigated as a matter of urgency, and that first rib resection is the procedure of choice if an appropriate lesion is found.

There does not appear to be a significant difference in symptomatic result between the transaxillary and supraclavicular surgical approaches, but in a first procedure with no evidence of damage to the subclavian artery transaxillary resection is recommended[11]. The operation is less time consuming, is said to be less painful[1], and has cosmetic advantages. We would strongly commend a separate supraclavicular incision if the subclavian artery is to be reconstructed.

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Spontaneous rupture of renal allografts: the importance of renal vein thrombosis in the cyclosporin era

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Spontaneous renal allograft rupture occurring within 14 days of transplantation occurred in 15 patients from 791 consecutive transplants. In each of eight patients treated with azathioprine and prednisolone there was pathological evidence of rejection and only two patients had thrombosis of the renal vein. Of the seven cases occurring in patients treated with triple therapy regimen (low dose cyclosporin, prednisolone and azathioprine), histological evidence of rejection was present in only three cases, but renal vein thrombosis was found in all seven. Spontaneous rupture of a transplanted kidney, a relatively uncommon complication, is more likely to be due to renal vein thrombosis than to rejection in the cyclosporin era.

Keywords: Renal transplantation, cyclosporin

Spontaneous renal allograft rupture is a relatively uncommon but life threatening surgical emergency[1]. Previous reports describe an incidence ranging from 0·3 per cent to 9·6 per cent of all transplants—most occurring in the first 3 weeks after transplantation and over 80 per cent being secondary to acute rejection[2–4]. Since the introduction of cyclosporin into clinical use in Oxford the commonest cause of renal allograft rupture is now renal vein thrombosis. This report describes all the cases of renal allograft rupture seen in the Oxford Transplant Unit since it was established in 1975.

Patients and methods

Between January 1975 and January 1989, 791 renal allografts were performed in Oxford, 730 from cadaver donors and 61 from living related donors. Over this period the immunosuppressive regimen has changed. Azathioprine with high dose steroids was used until 1978[5], when low dose steroids were introduced[6]. Cyclosporin, either alone or in combination with steroids, was used in clinical trials from 1979 to 1985[7] and since 1985 patients have received triple therapy with cyclosporin, azathioprine and steroids[8]. Rejection has been treated with 3–5 days of intravenous methylprednisolone at a daily dose of 1 g. Since 1980 a daily dose of 250 mg or 500 mg has been used depending on the body-weight of the patient and the severity of rejection. Highly sensitized patients (those with a positive crossmatch or with greater than 90 per cent panel reactivity) have been given prophylactic methylprednisolone for the first 3 postoperative days. Since 1985 a number of patients have been treated with antithymocyte globulin (ATG) for steroid resistant rejection[9]. Five patients have been given prophylactic ATG when it was felt that there was a high risk of primary renal vein thrombosis (i.e. using kidneys from donors with small or multiple vessels or donors under the age of 15 years) so that cyclosporin could be safely withheld for the first 7 postoperative days.

All operations were performed by experienced transplant surgeons. In general, all cadaver kidneys were retrieved with aortic and caval patches. The venous anastomoses were performed end to side to the external iliac vein using continuous 5/0 Prolene® (Ethicon Ltd., Edinburgh, UK). The arterial anastomoses were generally performed end to side to the external iliac artery using a continuous 6/0 Prolene suture. In the living related transplants and the occasional cadaver transplant where the aortic patch was damaged the donor renal artery was anastomosed end to end to the internal iliac artery. The uretoneocystostomy was performed using the Leadbetter–Politano technique[10]. Deliberate capsulotomy of the graft was not performed.

Allograft rupture was confirmed at exploration of the graft and was defined as a split in the renal capsule associated with haemorrhage when no identifiable injury to the capsule was noted at the time of harvesting.

Histological review was performed in all cases. The nephrectomy specimen was examined to determine the patency of renal vessels at the hilum of the kidney, and cut sections were examined for evidence of small vessel thrombosis and acute rejection using well defined and previously described criteria[11].

Results

Of 791 consecutive renal transplants 15 underwent spontaneous rupture—an incidence of 1·9 per cent. All occurred within the first 14 days after transplantation (nine within 7 days) and had been procured from cadaver donors. The mean recipient age was 35·3 years. There were ten males and five females, and of these, 13 were receiving their first transplant. Details of recipient age, donor age, individual immunosuppressive regimens and outcome are shown in *Tables 1* and *2*. The 'main cause of rupture' shown in *Table 1* was determined, at the time, in a weekly mortality and morbidity meeting. The occurrence of renal allograft rupture was not associated with either HLA-DR incompatibility between donor and recipient, or with the presence of a positive crossmatch before transplantation. Some of the cases with renal vein thrombosis have been described elsewhere in a previous report[12].

Presentation

All patients presented with sudden pain over the graft, and four patients experienced pain in the distribution of the femoral nerve, presumably due to acute compression by haematoma.

All patients whose allograft rupture was thought to be primarily due to rejection (see *Table 1*) were oliguric and dialysis dependent at the time of rupture. In contrast, the six patients who had renal vein thrombosis as the main cause of rupture were passing urine and were not dependent on dialysis at the time of rupture. Only one patient (case no. 600) had a percutaneous biopsy performed in the 48 h before rupture. The biopsy did not appear to be the cause of rupture since an extensive oblique tear in the kidney was found away from the biopsy site.

Operative findings and procedure

Eight ruptures occurred along the convex border of the graft. Of these, five involved the upper pole, one was an oblique rupture and one had ruptured near the hilum. In no instance was there any apparent technical problem, such as kinking or twisting of the vein due to poor placement of the graft. Nephrectomy was performed because of primary renal vein thrombosis (seven

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Table 1 *Details of patients with renal allograft rupture*

Case no.	Donor age (years)	Immunosuppression	Days from operation to rupture	Main cause of rupture	Outcome
28	22	HD steroid	6	Rejection	Nephrectomy
61	24	HD steroid	12	Rejection	Successful repair
136	28	LD steroid	9	Rejection	Successful repair
145	12	LD steroid	7	Rejection	Successful repair
243	18	LD steroid	3	Rejection	Nephrectomy
292	24	HD steroid	6	Rejection	Unsuccessful repair
361	35	LD steroid	4	Rejection	Successful repair
409	17	LD steroid	14	Rejection	Unsuccessful repair
547	6	Triple	7	RVT	Nephrectomy
548	6	Triple	14	RVT	Nephrectomy
555	53	Triple	5	Rejection	Nephrectomy
569	17	Triple	5	RVT	Nephrectomy
600	48	Triple	3	RVT	Nephrectomy
629	53	Triple	5	RVT	Nephrectomy
662	51	Triple	3	RVT	Nephrectomy

HD steroid, high dose steroid and azathioprine; LD, low dose steroid and azathioprine; Triple, triple therapy; RVT, renal vein thrombosis; Successful repair, functioning graft 6 months after transplantation; Unsuccessful repair, graft failure within 6 months of transplantation

Table 2 *Number of cases of renal allograft rupture in patients immunosuppressed with azathioprine and prednisolone or with cyclosporin, used either alone, in combination with steroid, or in a triple therapy regimen*

Immunosuppressive protocol	Total number transplanted	Number of ruptures
Azathioprine and steroids	365	8 (2·2)
Cyclosporin only	102	0
Cyclosporin and steroids	35	0
Triple therapy	289	7 (2·4)

Numbers in parentheses are percentages

cases), infarction secondary to rejection and uncontrollable bleeding and shock. Repair of the rupture with suture and haemostatic material was attempted in six cases.

Outcome

There were no deaths following graft rupture. In the six patients where repair was attempted, two required nephrectomy within the next 14 days for irreversible rejection. Secondary breakdown of the surgical repair of the kidney did not occur in these grafts. A further patient lost his graft 11 months after transplantation because of non-compliance with immunosuppressive drug therapy. The final three patients had good graft function and although one died from carcinoma of the lung, the other two are well 10 and 12 years after graft repair.

Eight patients who lost their grafts were subsequently retransplanted and six patients have grafts which are still functioning. Two grafts were lost in the early postoperative period, one due to primary renal vein thrombosis and the other to irreversible recurrent rejection.

Pathology

The results of histological examination are shown in *Table 3*. Where venous thrombosis was present it was almost always confined to the hilar veins. In cases 28 and 243 thrombus extended into the intrarenal veins, often as far as the corticomedullary junction and there was coexistent intrarenal arterial intimal fibrosis, thrombosis and fibrinoid; neither of these patients received triple therapy. Although intrarenal haemorrhage was a prominent feature in cases 548–600 and 662 the hilar and intrarenal arteries were patent with no evidence of thrombus or intimal fibrosis and features of cellular rejection were absent.

Table 3 *Histological findings in ruptured renal allografts*

Case no.	Artery occluded	Vein occluded	Interstitial haemorrhage	Vascular rejection	Cellular rejection
28	+	+	+	−	+
61	−	−	−	−	−
136	−	−	+	+	−
145	−	−	−	−	−
243	−	+	+	+	+
292	−	−	+	+	−
361	−	−	−	+	−
409	−	−	+	a	a
547	−	+	−	+	−
548	−	+	+	−	−
555	−	+	+	+	−
569	−	+	+	+	−
600	−	+	+	−	−
629	−	+	−	−	−
662	−	+	+	−	−

a, In case 409 the biopsy taken at the time of rejection consisted of medulla only, with interstitial haemorrhage and focal infarction. Nephrectomy was performed 28 days after rupture in this patient, and the kidney showed severe cellular and vascular rejection. +, Present; −, absent

Discussion

Before the introduction of cyclosporin rejection was the major cause of spontaneous renal allograft rupture[4,12]. Rejection causes an increase in both renal size and intrarenal pressure which may result in a split in the renal capsule, with extrusion of cortex and subsequent haemorrhage. The increase in renal size is often detectable by palpation[14,15], and oedema and cellular infiltration are seen histologically[11]. Direct measurement of intrarenal pressure has shown that there is often a rise from the normal level of less than 30 mmHg to over 80 mmHg during acute rejection[16]. The lower incidence of graft rupture associated with rejection in patients treated with cyclosporin is presumably due to the reduction in both the incidence and severity of rejection[17,18].

Cyclosporin may predispose transplanted kidneys to vascular thrombosis[12,14,15] by inducing a thrombotic tendency[19,20]. A report of an increased incidence of deep venous thrombosis in patients receiving cyclosporin[21] was not confirmed by a study from Oxford[22]. Renal vein thrombosis with graft rupture did not occur in 137 patients treated with either cyclosporin alone or cyclosporin and steroids, compared with seven cases of rupture in 289 patients treated with triple therapy. Further studies are required to investigate possible interactions between these drugs that might predispose predisposition to thrombosis.

Surgical repair of a ruptured graft where rejection is the cause is justified unless secondary renal artery or vein thrombosis has supervened. Thrombectomy might be attempted if exploration occurs within hours of the onset of the features of clinical rupture. In this series, and in previous reports, over half the patients in whom repair was attempted went on to enjoy good long term graft survival[3,4,19,23].

Loss of a graft from rupture, due to rejection or renal vein thrombosis, did not prevent subsequent successful retransplantation. A previous report was less optimistic[24] and one patient in this series (case no. 662) thrombosed the renal vein 5 days after retransplantation.

Spontaneous renal allograft rupture is an uncommon complication of renal transplantation and renal vein thrombosis in patients immunosuppressed with cyclosporin is now the commonest cause of rupture. Good long term graft function may be achieved in some by repair of the rupture provided that the renal vein is patent. In those with primary renal vein thrombosis graft loss is universal but retransplantation may be successfully performed at a later date.

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Addendum

Since this paper was accepted we have seen two more cases (numbers 862 and 885) of renal vein thrombosis and allograft rupture in patients receiving triple therapy immunosuppression. Prompt thrombectomy and repair of the renal capsule in one of these cases was not successful in prolonging graft survival.

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Hookers and French strippers: a technique for varicose vein surgery

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Although varicose veins of the lower limbs can cause pain, skin discoloration and even ulceration[1], a large proportion of varicose vein surgery is undertaken for cosmetic reasons. Despite this the surgical techniques used often yield far from cosmetic results. We report some modifications of standard operative methods which we have found to be both efficient and highly cosmetic.

Materials and methods

Meticulous preoperative marking of varicose veins, preferably by the surgeon, is essential. Once marked, a simple technique for determining the best direction for the planned incisions is to use a circular stamp (*Figure 1*) to outline circles over the proposed incision points[2]. This is done with the leg in the fetal position, flexed acutely at the knee and with the foot dorsiflexed (*Figure 2*). If the limb is then restored to the extended position the circles become ellipses (*Figure 3*). The direction of the long axes of the ellipses varies in different parts of the leg and also varies from person to person. Placement of small stab incisions along this longitudinal axis will mean that there is minimal tension on the incision, and will result in a virtually invisible scar. If the incisional guide line is drawn

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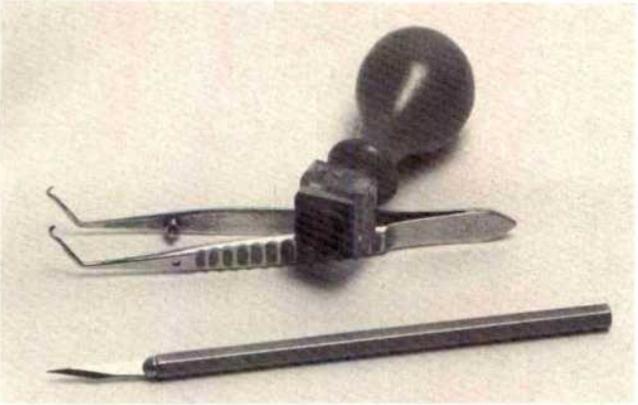

Figure 1 *Circular stamp, Beaver knife and hooked vein grasping forceps*

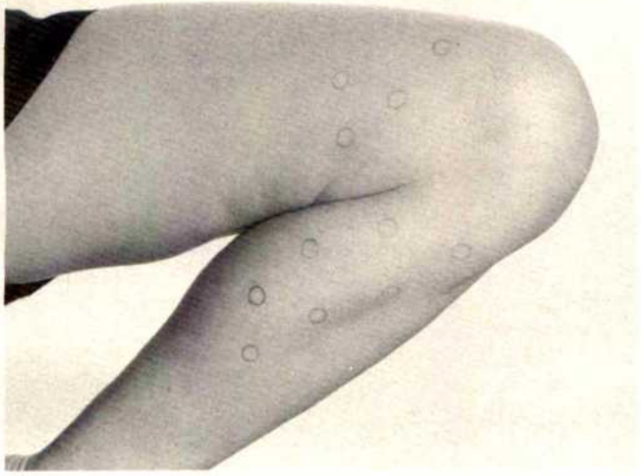

Figure 2 *Leg in fetal position used for marking with circular stamp*

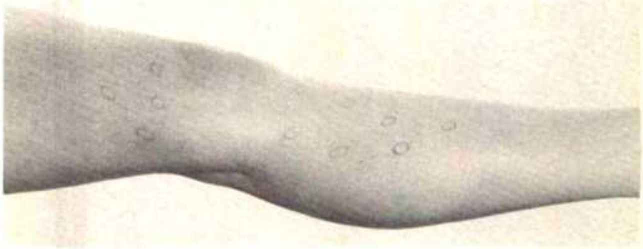

Figure 3 *Leg extended. Note that the circles have become ellipses*

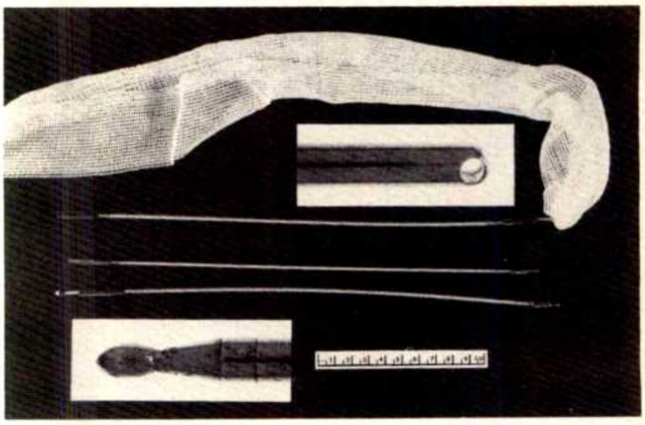

Figure 4 *Varicose vein stripper (three pieces to be assembled). From top to bottom: proximal portion with gauze swab inserted into hole in end (magnified); intermediate portion; distal portion with head (magnified); scale shown measured in cm*

with a pen, the position of the line will be maintained in whatever position the limb is subsequently placed. Interestingly, the lines of collagen deposition as originally described by Langer often differ quite significantly from the orientation of the incisions as indicated by this technique. The only situation in which the stamping procedure is not appropriate is across joint lines where better results are achieved with transverse rather than longitudinal incisions.

For patients with saphenofemoral incompetence, the above-knee segment of the long saphenous vein is stripped and further above and/or below-knee varicosities removed by multiple avulsions. Using a standard groin dissection, the long saphenous vein is identified and the stripper shown in *Figure 4*, which was originally developed by Dr Jean Hardillier, a well known Parisian surgeon, and is produced in the UK by Abbey Surgical Ltd., Mitcham, Surrey, is introduced and passed to a point just below the knee. Because the head of the stripper is no wider than its shaft, only a small incision is necessary to retrieve it and the incision is placed in the direction indicated by one of the elliptical marks. An unravelled swab is attached to a hole in the proximal end of the stripper (*Figure 4*), so that passage of the instrument distally allows stripping of the long saphenous vein with immediate compression of the tunnel by the swab, thereby reducing bleeding and haematoma formation. Distal division of the long saphenous vein then precedes its retrieval from the groin wound, together with both swab and stripper. Not infrequently the saphenous vein is turned inside out, but this is of no consequence.

Multiple avulsions are undertaken using a Beaver knife (McCarthy Surgical, Dagenham, Essex, UK) (*Figure 1*) to make 2 mm incisions within the premarked ellipses. Specially constructed hooked forceps (produced to order by Abbey Surgical Ltd., Mitcham, Surrey, UK) (*Figure 1*) are then used to hook out segments of vein from within each wound. The hooked forceps are gently introduced through each incision, and turned in each direction without pulling against the wound edges until the vein is grasped. Once delivered, each segment of vein is seized by mosquito forceps and the avulsions completed without recourse to inserting the forceps into the wound and, as so often happens, causing inadvertent stretching. Apposition of wound edges with Steri-strips (3M, St Paul, Minnesota, USA) is followed by bandaging with elasticated crepe dressings. Closure of the groin wound with subcutaneous Vicryl® and subcuticular Prolene® (Ethicon Ltd., Edinburgh, UK) completes the procedure.

Discussion

The described modifications of standard techniques have produced very satisfactory cosmetic results in our practice and we feel that they represent a significant advance in the surgical treatment of lower limb varicosities.

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Vacuum drainage of groin wounds after vascular surgery: a controlled trial

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A pilot study of 100 consecutive groin wounds after vascular surgery demonstrated lymph leaks in 12 per cent. Lymph leak was significantly associated with wound infection and with prolongation of in-patient stay. A controlled trial was therefore instituted to assess the influence of vacuum drainage in groin wound healing. One hundred and twenty-seven wounds were randomized to drainage (n = 65) or no drainage (n = 62) and the wounds were examined 'blind' by independent observers. No difference in the incidence of lymph leakage or wound infection was noted between the two groups. The routine use of suction drainage for groin wounds in vascular surgery is unnecessary.

Keywords: Wound infection, drainage, vascular surgery

The main lymphatic trunks of the legs converge in the inguinal region[1]. They are inevitably disrupted during femoral artery exploration as part of many vascular surgical operations. Such disruption may result in clinically important lymph leakage. A lymph fistula or cyst has a potential for wound infection with subsequent graft infection and failure. Although quite common, lymph leakage after vascular procedures in the groin has seldom been evaluated in the literature[2–4]. In a pilot study, the extent of lymph leakage and other complications in a consecutive series of groin wounds were defined. This was followed by a randomized, blind, controlled trial of the influence of suction drainage on lymph leakage and wound infection after femoral artery exploration.

Patients and methods

Pilot study

One hundred consecutive groin wounds were studied in 83 patients who underwent femoral artery exploration as part of a vascular surgical operation during a period when it was routine practice to use vacuum wound drains (Redivac®, Biomet Ltd., Bridgend, UK). The wounds were assessed by a single observer, from the third day after surgery until the wound was soundly healed or until discharge from hospital, whichever was the later. For this pilot study and the subsequent clinical trial, a lymph fistula was defined as a continued leak from the wound of clear fluid for more than 48 h. A lymph cyst was defined as a swelling under the wound developing two or more days after surgery from which clear fluid was obtained on needle aspiration. The biochemical differentiation of lymph fluid from resolving haematoma was found to be inconsistent and so a clinical distinction was preferred. Wound infection was recorded if cellulitis or discharging pus was noted. Bacteriological examination was carried out where clinically indicated.

Statistical significance was assessed using χ^2 analysis with Yates' correction and the Mann–Whitney *U* test where appropriate.

Clinical trial

Consecutive patients undergoing a variety of vascular surgical operations involving a longitudinal groin incision for femoral artery exploration were entered into the trial. In patients undergoing bilateral procedures only one wound was randomized and included in the trial. All operations were carried out by the same consultant surgeon using a standard closure technique comprising two layers of continuous 3/0 subcutaneous Vicryl® (Ethicon Ltd., Edinburgh, UK) and continuous 3/0 monofilament nylon to the skin. Groin wounds were randomized using sealed envelopes to have either vacuum drainage or no vacuum drainage. A narrow bore Redivac® drainage system was used in all drained wounds and was removed 48 h after surgery. A small adhesive dressing was placed over the drain track. A similar dressing was placed adjacent to the wound where no drain had been used. An independent observer, who was unaware of the results of randomization, assessed the wounds daily from 48 h after operation.

Results

Pilot study

The different procedures requiring femoral artery exploration during the course of the pilot study are shown in *Table 1*. Lymph cyst or fistula occurred in 12 of the 100 wounds studied (*Table 2*). Wound infection was recorded in 14 wounds, five of which had lymph leakage, and this correlation is statistically significant ($\chi^2 = 6{\cdot}25$; $0{\cdot}02 > P > 0{\cdot}01$). In addition to its correlation with wound infection, lymph leakage was also associated with a prolonged hospital stay. Excluding nine infected wounds without lymph leakage, the mean stay of patients with uncomplicated wounds was 12·4 days (median 11 days; range 6–26 days) and the mean stay of patients with lymph leakage was 20·4 days (median 22 days; range 11–30 days). This difference was significant ($U = 1731{\cdot}0$; $P = 0{\cdot}0001$). For those patients who had bilateral groin explorations, only the wound which took longer to heal was included in the analysis and so the numbers of patients in each group were necessarily smaller (11 with and 57 without lymph leakage). In addition, some wounds could not be followed up to healing and discharge from hospital, as two patients died (one wound with no complications, one infected

Table 1 *Procedures involving femoral artery exploration in the pilot study*

Procedure	Number
Aortofemoral graft	28
Iliofemoral graft	10
Local femoral artery procedure*	35
Femoropopliteal graft	
Prosthetic	8
Reversed vein	14
In situ vein	5

* Includes femoral embolectomy, profundoplasty, femorofemoral cross-over, etc.

Table 2 *Number of wound complications in 19 wounds in the pilot study group*

Complication	Number
Lymph fistula	6
Lymph cyst	6
Erythema	6
Discharge	8

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Table 3 *Numbers of operative procedures in those with and without drainage*

Procedure	Drainage	No drainage
Autogenous vein graft (femoropopliteal bypass)	14	15
Prosthetic graft (aortofemoral and femoropopliteal bypass)	39	37
No graft (local procedure)	12	10

Table 4 *Numbers of wound complications in the groups with and without drainage*

Complication	Drainage	No drainage
Lymph fistula	17	18
Lymph cyst	5	6
Erythema	49	48
Wound discharge	11	12

wound), and three patients were transferred to other units (three wounds with no complications, one infected wound). There was no preponderance of major procedures or other factors in the lymph leakage group to explain its association with prolonged hospital stay. Interestingly, the two most serious cases of lymph leakage occurred after straightforward femoral embolectomy.

During the pilot study there was a clinical impression that suction drainage might promote the leakage of lymph from the severed ends of the lymphatic channels around the femoral artery Because of the significant association of wound infection and prolonged hospital stay with lymph leakage, a prospective trial of the influence of suction drainage on lymph leakage was instituted.

Clinical study

A total of 127 groin wounds in 99 patients were randomized, of which 72 were right-sided and 55 were left-sided, and 65 were drained and 62 were not. The groups were comparable in respect of mean age (66 and 68 years respectively) and distribution of operative procedures (*Table 3*). There were 54 men in the group with drainage and 42 in the group without drainage (*Table 3*). No significant difference was noted in the incidence of wound infection, lymph cyst or lymph fistula between the two groups (*Table 4*).

Discussion

The pilot study identified lymph leakage as an important problem following femoral artery exploration. A correlation between lymph leakage and both wound infection and prolonged hospital stay was demonstrated. Wound infection after implantation of graft material is potentially disastrous and any factor which might predispose to infection must be avoided. Watson *et al.*[5] demonstrated bacterial contamination of 33 per cent of suction drainage systems, used in vascular and breast surgery wounds, which were left *in situ* for more than 48 h. Increased wound infection rates associated with vacuum drainage have been noted in randomized trials in other surgical procedures such as cholecystectomy[6]. This background, combined with a clinical impression that vacuum drains may actually promote lymph leakage and hence wound infection, prompted the present prospective study.

The routine use of vacuum drainage for vascular surgical wounds is common in many centres. These drains are uncomfortable for the patient and are an extra cost. While the present prospective trial has not demonstrated an increased incidence of either lymph leakage or wound infection in the drained group, as was initially suspected from the observations in the pilot study, neither has it demonstrated any advantage in the routine use of suction drains in preventing these complications. Drains are also used in vascular surgery to minimize the possibility of wound haematoma. However, the only wound haematoma requiring intervention in the present series occurred in a drained wound during the pilot study.

The results described suggest that the routine use of vacuum drainage is unnecessary in longitudinal vascular surgical wounds made to expose the femoral artery.

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Flow cytometric and histological analysis of ductal carcinoma *in situ* of the breast

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Using archival paraffin wax embedded tumour we have investigated histological grade, DNA ploidy, S phase fraction and proliferative index in 74 patients with symptomatic ductal carcinoma in situ *(DCIS) of the breast. Nine patients developed local recurrence, six invasive in character. No patients with the cribriform subtype of DCIS developed local recurrence. The cribriform subtype showed a significantly lower rate of DNA aneuploidy and a lower proliferative index than the other subtypes. Cribriform tumours were almost exclusively well differentiated in contrast with the comedo and solid variants. Our results suggest the cribriform variant is less aggressive than other subtypes of DCIS. This has possible implications for management of these lesions.*

Keywords: Breast cancer, ductal carcinoma, in-situ flow cytometry

In clinical practice pure ductal carcinoma *in situ* (DCIS) of the breast is encountered infrequently, comprising 1–5 per cent of reported series of breast carcinoma[1–3]. Before the introduction of mammography this condition would present to the breast clinic, usually as a palpable breast lump. The association of microcalcification with DCIS has led to a higher frequency of detection of this condition in mammographic breast screening programmes. The results of these programmes show that smaller and more prognostically favourable tumours, including DCIS, are more frequently encountered than with symptomatic presentation.

The optimal treatment for DCIS is unknown. Treatment by tumorectomy with or without irradiation results in subsequent local recurrence in a substantial number and this recurrence can be invasive in character In addition, DCIS is frequently a multifocal disease.

A number of subtypes of DCIS are recognized pathologically. The comedo subtype appears more aggressive histologically and thymidine labelling studies[4] show such tumours to have a higher proliferative index. The purpose of this study was to investigate the various histological subtypes of DCIS with respect to biological features (histological grade, nuclear DNA content and cell cycle analysis) all of which have been shown to be of prognostic value in invasive breast cancer[5–11].

Patients and methods

We have identified 74 patients with DCIS presenting to the breast clinic at the Nottingham City Hospital between 1973 and 1988 Using hospital case notes the patient's age, presenting symptom(s), relevant clinical findings and the type of surgery were defined in each case. Tumour size was not available for all patients. Less than half the patients had preoperative mammography and thus radiological details regarding tumour multifocality was deficient

Treatment type

There were five surgical treatments used. simple or subcutaneous mastectomy with node sampling, wedge mastectomy, cone excision or lumpectomy and irradiation (45 Gy and 15 Gy boost to the tumour bed using a 4 or 6 MV linear accelerator over 6 weeks). Wedge mastectomy as practised in Nottingham, and used in patients over 70 years of age, refers to amputation of the breast at the chest wall and primary skin closure without any dissection of skin flaps. Cone excision used in patients with Paget's disease of the nipple consists of complete excision of the nipple/areola complex with a cone of underlying breast tissue

Patient follow-up

Patients were reviewed in a breast clinic and accurate information on subsequent recurrence and overall patient survival was obtained

Histology and flow cytometry

Paraffin embedded tumour tissue was available for all patients A 30 μm section was cut from the tumour block, immediately followed by a 5 μm section which was stained with haematoxylin and eosin. One pathologist (I.O E) reviewed these sections and categorized the tumours into subtypes; tumours with evidence of microinvasion were excluded from the study. Four main subtypes were identified cribriform, solid, comedo and micropapillary. Tumours in which there was less than 80 per cent of any particular subtype were classified mixed Histopathological grading was carried out by the same pathologist, using a modification of the technique of Bloom and Richardson[5].

The 30 μm section was used for flow cytometry, The method of dissociation of tumour cell nuclei was identical to that first described by Hedley *et al.*[12] In brief; the tumour section was dewaxed with xylene and rehydrated through an alcohol gradient. Pepsin digestion and vortexing allowed dissociation of the nuclei which were then filtered through a 60 μm stainless steel mesh to remove debris and stained with the nucleic acid dye DAPI (4'6'diamidino-2-phenylindole).

The stained nuclei were analysed in a Becton Dickinson FACS (fluorescence activated cell sorter) analyser (Becton Dickinson UK Ltd., Oxford, UK) using a mercury arc lamp producing ultraviolet light below 375 nm to excite fluorescence. A minimum of 20 000 nuclei were analysed for each sample and a DNA histogram derived.

Flow cytometry histogram analysis

The assumption made is that DNA staining is stoichiometric and thus fluorescence intensity is proportional to DNA content Lymphocytes and stromal cells act as an internal standard and these 'diploid' controls are set in channel number 50 If only one G_0G_1 peak is noted then the tumour cells and control cells occupy the same modal channel number If a second distinct peak is noted, then this represents a population of DNA 'aneuploid' tumour cells. To avoid misinterpretation of diploid G_2M peaks as aneuploid peaks, a cut-off of >15 per cent of the total population of cells was required. Tumours with more than one aneuploid population were termed multiclonal

The DNA index is the ratio of the channel number of the tumour cell peak to the internal control cell peak. By definition a diploid tumour has a DNA index of 1 0. An aneuploid tumour has a DNA index greater than (or less than) 1·0

Using a computer interfaced to the FACS analyser markers were set and the number of cells in the different compartments of the cell cycle determined. The S phase fraction and the G_2M fractions were calculated as percentages of the whole cell population measured

For aneuploid tumours the internal control cells are 'gated' out and the 'aneuploid' peak and its cell cycle are treated in the same way as for a diploid tumour The coefficient of variation for the G_0G_1 peak in channel 50 was determined in each case, this being a measure of

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Table 1 *Histological grade distribution within the subtypes of ductal carcinoma* in situ *(DCIS)*

	Histological grade			Cribriform *versus* other subtype χ^2 test
DCIS subtype	1	2	3	*P*
Cribriform	14	1	0	–
Solid	1	2	11	<0·001
Comedo	0	1	17	<0·001
Micropapillary	2	2	0	n.s.
Mixed	9	10	4	<0·01

Table 2 *DNA ploidy distribution within ductal carcinoma* in situ *(DCIS) subtypes* (n = 74)

DCIS subtype	Diploid/ near diploid	Aneuploid/ multiclonal	Cribriform *versus* other subtype (Fisher's exact test)
Cribriform	13	2	—
Solid	6	8	0·017
Comedo	7	11	0·006
Micropapillary	1	3	0·037
Mixed	13	10	0·052

Table 3 *S phase fraction distribution within ductal carcinoma* in situ *(DCIS) subtypes* (n = 46)

DCIS subtype	Mean S phase fraction (%)	Median S phase fraction (%)
Cribriform	5·0	3·5
Solid	8·4	6·5
Comedo	12·3	9·5
Micropapillary	6·5	6·5
Mixed	6·9	6·8

No significant differences by Mann–Whitney *U* test between subgroups

resolution. Finally, the proliferative index of the tumours is calculated. This is the sum of the percentage of the total cell population in the S and G_2M compartments[13].

Results

Histology and flow cytometry

There were 23 mixed, 18 comedo, 15 cribriform, 14 solid and four micropapillary tumours. Although the morphology of the comedo and solid variants is very similar, the two were analysed separately for the purpose of subsequent study.

The relationship between tumour subtype and histopathological grade is seen in *Table 1*. The cribriform subtype tumours were largely grade 1 or well differentiated and 11 of 14 solid and 17 of 18 comedo tumours were grade 3 or poorly differentiated. The levels of significance between the cribriform and other subtypes are shown in *Table 1*.

The mean coefficient of variation for the G_0G_1 peak in channel 50 of the flow cytometric DNA histogram was 4·4 per cent. In the analysis of DNA ploidy distribution within the tumour subtypes diploid and near diploid tumours (DNA indices 1·0–1·3) are distinguished from aneuploid and multiclonal tumours (DNA index > 1·3 or 2 or more aneuploid peaks). The results are seen in *Table 2*, which demonstrate that 13 of 15 cribriform tumours were diploid or near diploid. The other subtypes had a significantly higher proportion of aneuploidy or multiclonality except for the mixed subtype.

Forty-six of the 74 DNA histograms were amenable to the determination of S and G_2M phase fractions. The mean and median S phase fractions of the subtypes are shown in *Table 3*. Although the mean and median S phase fractions are lowest for the cribriform tumours this just fails to reach statistical significance by the Mann–Whitney *U* test. When the proliferative indices of the cribriform tumours are compared with the others, as in *Figure 1*, however, there are significantly lower values for the cribriform subtype. The largest difference was found between the cribriform and comedo subtypes.

Clinical

The mean and median ages of the 74 patients at presentation was 52·9 and 53·5 years respectively (range 28–79 years). The presenting symptom(s) are seen in *Table 4*. The 14 patients who presented with soreness and crusting of the nipple were diagnosed as having Paget's disease by nipple biopsy. There was underlying DCIS (comedo or solid) in all cases but no evidence of invasive tumour in multiple histological sections. Ten of the 14 patients were treated by simple mastectomy and four by cone excision.

The median patient follow-up was 70 months (range 2–180 months), during which time nine patients developed local recurrence. We have defined this as recurrence in the skin flaps if mastectomy had been performed or in the parenchyma or skin of the treated breast if a lesser procedure. Of these nine, three were DCIS and six invasive cancer. One patient whose initial treatment was simple mastectomy had uncontrolled local recurrence on the chest wall. The nine patients with local recurrence had solid, comedo or mixed DCIS subtypes. None of 15 cribriform or four micropapillary tumours have recurred. *Table 5* details the number of patients undergoing the different treatments within each tumour subtype.

An analysis of the available data with respect to menopausal status, location of the tumour in the breast, length of patient follow-up, completeness of excision, tumour size and multifocality was made. None of these parameters was significantly different between subgroups or related to subsequent prognosis.

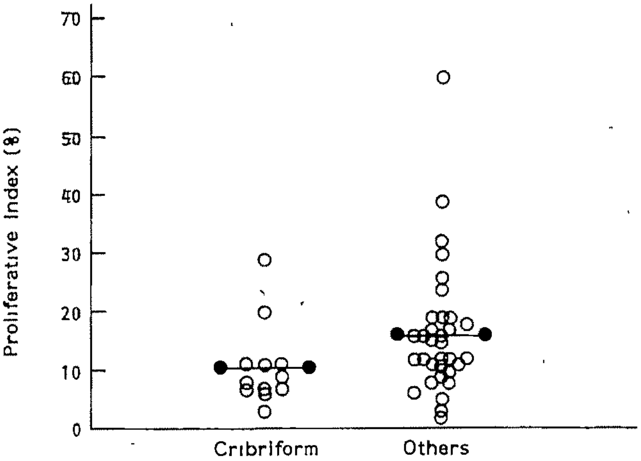

Figure 1 *Proliferative indices of cribriform and other subtypes of ductal carcinoma* in situ. *Mann–Whitney* U *test,* Z = −2·23, P = 0·026

Table 4 *Presenting symptoms* (n = 74)

Symptom	*n*
Breast lump	38
Sore/crusted nipple	14
Nipple discharge	10
Mammographic abnormality	5
Nipple discharge and lump	5
Breast pain	2

Table 5 *Initial surgical treatment divided by subtype of ductal carcinoma* in situ *(DCIS)*

	Operation type				
DCIS subtype	Simple mastectomy	Subcutaneous mastectomy	Wedge* mastectomy	Cone* excision	Excision and radiotherapy
Cribriform	8	5	2	0	0
Solid	8	1	1 (1)	4 (2)	0
Comedo	12	3 (1)	0	0	3 (1)
Micropapillary	2	1	0	0	1
Mixed	10 (1)	9 (1)	0	0	4 (2)
Local recurrence	1	2	1	2	3

Values in parentheses indicate local recurrences; *see text

Discussion

The optimal treatment for DCIS is not known. Twenty-five to 30 per cent of women with only microscopic foci of DCIS, subjected to no more than biopsy, will develop an ipsilateral invasive carcinoma within 15 years[14]. Mastectomy may effect cure in the vast majority of these patients but would overtreat a number of patients in whom DCIS would not have progressed to invasive carcinoma.

Because of the relative infrequency of pure DCIS compared with invasive cancer, previous studies have tended to group together the various subtypes as one entity. It is well established, however, that some subtypes of invasive breast cancer have a much better prognosis than others[15,16]. This study has investigated a number of potential prognostic parameters in symptomatic DCIS and demonstrates important differences between the subtypes

In invasive breast cancer histological grading has been shown to be an important prognostic factor[5,6]. Patients with well differentiated tumours have better overall and disease-free survival compared with those with poorly differentiated tumours In DCIS nuclear pleomorphism and mitotic rate are most abnormal in the comedo variant[17,18]. In this study all but one of the 15 cribriform tumours was well differentiated whereas 87 5 per cent of the solid and comedo subtypes were poorly differentiated, suggesting that cribriform DCIS is likely to behave less agressively Histological grading, however, is subjective and is influenced by the criteria used to designate a specific tumour type. The more objective measures of DNA ploidy, S phase fraction and proliferative indices in this study imply that the cribriform variant is less aggressive.

DNA ploidy has been shown[7,8] to be of independent prognostic significance in invasive breast cancer. Others[9], demonstrating an association between diploid tumours and favourable prognostic parameters (good histological grade and oestrogen receptor positivity) have not shown DNA ploidy to be an independent prognostic factor. DNA aneuploidy appears to give important prognostic information in several pre-malignant states It has been shown to predict the likelihood of the development of invasive malignancy in borderline lesions of the ovary[19] and increasing DNA aneuploidy is associated with increasing degrees of dysplasia in cervical intraepithelial neoplasia[20]. Carpenter and colleagues[21] investigated the relevance of DNA content in screen detected DCIS and proliferative atypia using static cytometry. Their results suggested that DNA aneuploidy may be of value in predicting the most biologically aggressive lesions. Our results demonstrate that the cribriform subtype was most likely to show minimal nuclear DNA content aberrations. A higher proportion of aneuploidy was seen in the other subtypes, including the micropapillary variant, thought to be a less aggressive tumour (and frequently grouped together with the cribriform subtype). Multiclonal tumours were also seen in the solid, comedo and mixed subtypes but not in the cribriform or papillary tumours

The S phase fraction studies in invasive breast cancer have been largely carried out by thymidine labelling. Meyer and Hixon[10] and Tubiana and colleagues[11] have demonstrated that tumours with a high labelling index, indicating rapid cell proliferation, had a diminished overall and disease free survival. Flow cytometrically derived S phase fraction does correlate with S phase fraction determined by thymidine labelling[22], although the former method consistently overestimates the proportion in that cell compatment. Flow methods have the advantage of being much less protracted.

Our results suggest that there are differences in the aggressiveness of DCIS depending on subtype. Meyer[4] has shown in thymidine labelling studies that the rate of proliferation in the cribriform subtype of DCIS is lower than that of the comedo variant and that for the solid type is in between. In this study the mean S phase fraction of each subtype, although not statistically different, reflects a similar trend. The proliferative indices of the cribriform subtype, however, are lower than the others ($P=0{\cdot}026$, *Figure 1*). The overlap seen in the ranges of proliferative indices in *Figure 1* would limit the predictive value of this measurement.

The treatments used in these patients were varied, making interpretation of the subsequent local recurrence rates difficult. There were no local recurrences in the cribriform subgroup but none of these patients underwent cone excision (as Paget's disease was not associated with this particular subtype) or local excision and radiotherapy. There were, however, three local recurrences in the 34 patients with mixed or comedo DCIS undergoing simple or subcutaneous mastectomy with node sampling and two had invasive tumour No firm conclusions can be drawn from this data but cribriform tumours appear less likely to recur. Indeed Meyer[4] showed that cribriform–papillary intraduct carcinoma is a slowly proliferating lesion giving rise to slowly proliferating invasive carcinomas with relatively high levels of oestrogen and progesterone receptors.

Mammographic screening will detect more DCIS, although it is possible that these lesions may have a different natural history compared with the symptomatic DCIS investigated in this study. Our results demonstrate differences in the biology of the subtypes of DCIS of the breast and this has possible implications for treatment planning.

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Clinical trial of calcium alginate haemostatic swabs

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The influence of a new haemostatic material on surgical bleeding was evaluated in 100 patients who were prospectively randomized to either normal surgical gauze or calcium alginate swabs used throughout cholecystectomy ($n=40$), *simple mastectomy* ($n=18$) *or inguinal hernia repair* ($n=42$). *Overall, median* (*range*) *blood loss was 91*(*3–329*) *ml for gauze and was significantly reduced by calcium alginate swabs to 72*(*2–181*) *ml* ($P<0{\cdot}05$). *Unexpectedly, operation times were also shortened from 45*(*17–95*) *min for gauze to 35*(*13–70*) *min with calcium alginate swabs* ($P<0.02$). *This reduction in blood loss and operating time was greatest for mastectomy, was still statistically significant for cholecystectomy, but was unimportant in inguinal hernia repair. Calcium alginate haemostatic swabs may become routine in major surgery, particularly where blood loss leads to the need for transfusion.*

Keywords: Haemostatic materials, calcium alginate, surgical haemostasis

Blood loss is inevitable during surgery with a large part of the surgeon's time spent controlling haemorrhage which would otherwise obscure the view and in major surgery lead to blood transfusion. Gauze swabs have been used for centuries, presumably as they are cheap, staunch the flow of blood by direct pressure and provide a surface for contact activation of coagulation.

Calcium alginate (BritCair Ltd., Aldershot, UK) was first introduced as a wound dressing; in this study it is evaluated as a possible surgical haemostat. On contact with blood, calcium ions are released in exchange for sodium ions and activate coagulation by stimulating platelets and the clotting factors VII, IX and X[1]. The sodium alginate formed following ion exchange is a gel which does not stick, so that when the swab is removed the underlying coagulum is not disturbed. This sodium alginate is absorbable so that limited quantities may be safely left *in situ*. The importance of Ca^{2+} ion release in the haemostatic action of this material was demonstrated by studies on whole blood coagulation and platelet aggregation. The results showed that coagulation and platelet function was activated with increasing Ca^{2+} content of alginates[2]. Calcium alginate with 99 per cent Ca^{2+} ions was most haemostatic *in vitro* and *in vivo*. In a comparative study, calcium alginate controlled bleeding in experimental liver lacerations significantly faster than either Surgicel (oxidized cellulose, Johnson and Johnson, Ascot, UK) or Medistat (porcine collagen, Genetic Laboratories)[3]. As calcium alginate materials can be manufactured inexpensively, and in bulk, we studied the possibility that standard surgical gauze may be replaced with calcium alginate swabs in a range of general surgical procedures.

Patients and methods

One hundred patients undergoing the routine general surgical procedures of cholecystectomy, simple mastectomy or inguinal hernia repair were randomized before operation to either normal surgical gauze or calcium alginate swabs manufactured in the same size ranges. Randomization was carried out separately for each operation using batches of 40 sealed envelopes. All operations were performed by experienced (post-FRCS) surgeons from one of three surgical teams who modified their normal technique slightly to utilize the potential benefits of calcium alginate while still using both materials in a similar way. Larger vessels were sealed by diathermy or ligature as usual, but surgeons were encouraged to leave alginate swabs on oozing surfaces rather than using the diathermy. Operation time was measured from skin incision to placement of the last suture. The number of swabs used was recorded and blood loss accurately measured.

A tube drain was inserted following all the cholecystectomies and suction drains for the mastectomies. Postoperative drainage and any complications occurring within 6 weeks of surgery were recorded.

Measurement of blood loss

All blood loss throughout the operation was collected either onto the swabs or by suction into a bottle containing 500 ml of heparinized saline. The used swabs were thoroughly washed in 2·5 l of heparinized saline before adding the fluid from the sucker bottle and mixing. A 20 ml sample of this diluted blood was taken, haemolysed with potassium cyanide and haemoglobin measured using a Coulter haemoglobinometer. Total blood loss (ml) was then calculated by comparing this haemoglobin with the haemoglobin of 1 ml of preoperative venous blood similarly diluted.

Analysis of results

Results were expressed as median (range) with any differences between surgical gauze and calcium alginate patients analysed statistically using the non-parametric Mann-Whitney U test.

Results

Forty patients undergoing cholecystectomy, 18 simple mastectomy and 42 inguinal hernia repair were randomized to either gauze or calcium alginate. The groups were similar with respect to age, sex and weight (*Table 1*).

Table 1 *One hundred patients randomized to standard gauze or calcium alginate swabs during surgery*

	Gauze	Calcium alginate
Cholecystectomy		
No. of patients	20	20
Male/female ratio	5/15	4/16
Age (years)	52·0 (4·0)	46·0 (3·7)
Weight (kg)	71·0 (3·6)	65·0 (3·4)
Mastectomy		
No. of patients	11	7
Age (years)	55·8 (3·1)	61·7 (4.5)
Breast weight (g)	539 (56)	471 (61)
Hernia repair		
No. of patients	21	21
Male/female ratio	20/1	19/2
Age (years)	62·0 (3·5)	61·5 (3·3)
Weight (kg)	67·6 (3·5)	72·2 (2·5)

Results expressed as mean (s.e.m)

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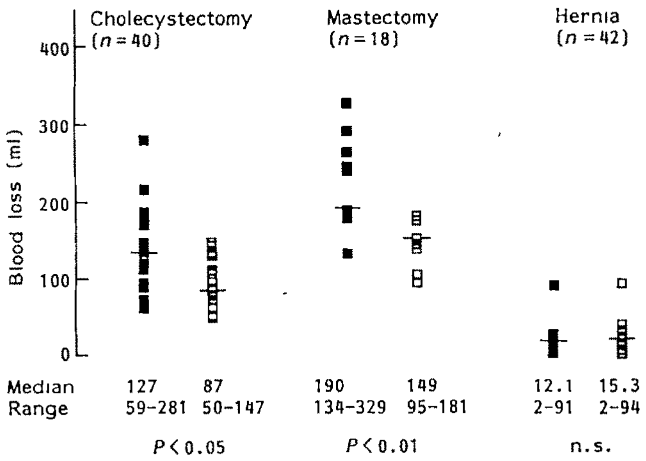

Figure 1 *Operative blood loss for each individual patient measured precisely in millilitres Calcium alginate reduced bleeding significantly in those patients undergoing cholecystectomy and mastectomy but not hernia repair* ■, *gauze*, □, *calcium alginate*

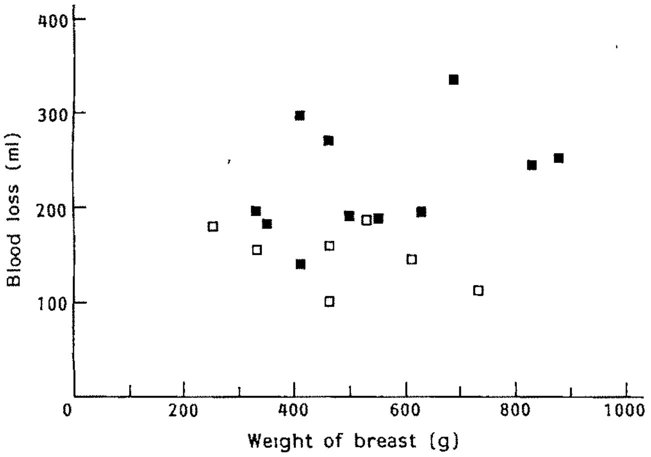

Figure 2 *Comparison of blood loss with weight of breast removed at mastectomy. Blood loss was less when using calcium alginate irrespective of breast weight* ■, *gauze*, □, *calcium alginate*

Blood loss

Overall, median (range) blood loss was 91(3–329) ml for gauze and was reduced to 75(2–181) ml when calcium alginate swabs were used ($P<0\cdot05$). When the individual operations were considered there was no important difference between gauze and calcium alginate in hernia repair but bleeding was reduced significantly and by approximately one-third when calcium alginate swabs were used for both cholecystectomy and mastectomy (*Figure 1*). The median (range) blood loss for cholecystectomy was 127(59–281) ml using gauze compared with only 87(50–147) ml using calcium alginate ($P<0\cdot05$). In simple mastectomy, which involves considerable tissue oozing, a median (range) of 190(134–329) ml of blood was lost with gauze compared with 149(95–181) ml with calcium alginate ($P<0\cdot01$). After mastectomy, all breasts were weighed and there was no correlation between breast weight and blood loss (*Figure 2*). Bleeding during hernia repair was minimal with a median (range) of 12·1(2–91) ml for gauze and 15·3(2–94) ml for calcium alginate.

Number of swabs used

The number of swabs used reflected the blood loss with fewer alginate swabs than gauze swabs being needed. Swab use was reduced significantly in cholecystectomy with a median (range) of 7(5–12) for calcium alginate compared with 10(6–18) for gauze swabs and mastectomy with 15(7–19) and 24(12–32) swabs used respectively ($P<0.05$). There was no difference for hernia repair with a median of three swabs of either type used in each operation.

Operation time

The minor modification in surgical technique involved in using calcium alginate swabs did not prolong operation time (*Figure 3*). In fact, the median (range) operation time for all 100 patients was 45(17–95) min for gauze and 35(13–70) min when calcium alginate swabs were used ($P<0\cdot02$). Again, the benefits of calcium alginate swabs were confined to cholecystectomy and mastectomy with operating time for cholecystectomy reduced to only 45(33–70) min compared with 55(40–90) min for standard gauze swabs ($P<0\cdot002$). In mastectomy, operations using calcium alginate were shortened by a mean of 10 min 36(33–60) min compared with 46(38–95) min for gauze ($P<0\cdot03$). There was no significant difference in operating time for hernias with the calcium alginate operations being a mean of only 1 min shorter 23(13–45) min compared with 24(17–45) min for gauze.

Postoperative drainage and complications

One patient in the gauze group had a postoperative biliary leak which stopped spontaneously after 10 days, having drained 3 l of bile. Even when this patient was excluded, the median postoperative drainage was significantly less when cholecystectomy had been carried out using calcium alginate; 25(0–400) ml compared with 120(0–800) ml for gauze ($P<0\cdot02$) If more than 100 ml of fluid drained on the second postoperative day the drains were not removed. On this basis one patient in the alginate group and four patients in the gauze group required their drains to be left in longer. There was no significant difference in drainage following mastectomy with a median (range) of 250(60–1000) ml for gauze and 260(90–1000) ml for calcium alginate. There were no differences in postoperative complications between the two groups with three wound infections, two wound haematomas and two inflamed wounds in the gauze group compared with one of each of these in the patients where calcium alginate swabs were used.

Discussion

These results demonstrate that swabs manufactured from haemostatic materials such as calcium alginate may be used to reduce operative bleeding in a variety of operations. As less blood was lost, fewer of the haemostatic calcium alginate swabs

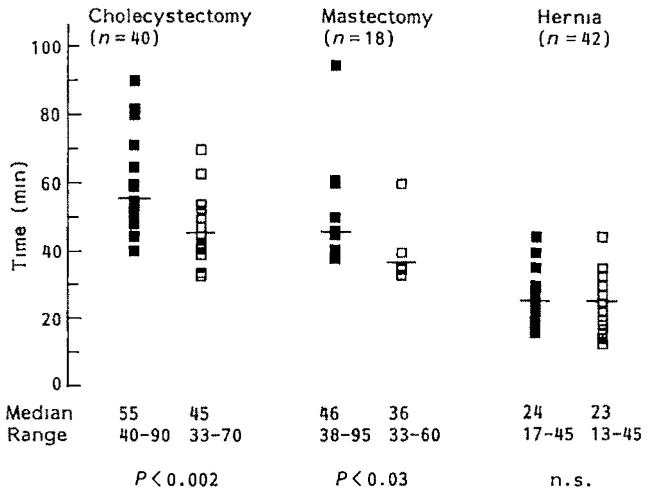

Figure 3 *The duration time for surgery (min) was unexpectedly shorter for all procedures when calcium alginate swabs were used, but only significantly so for cholecystectomy and mastectomy.* ■, *gauze*; □, *calcium alginate*

were needed. We had initially been concerned that by using calcium alginate swabs in the manner recommended, surgeons may prolong operation times but, in practice, we found that by reducing blood loss, the surgery proceeded more rapidly. Calcium alginate has been shown to be four times as absorbent per unit weight than gauze which may also have reduced the number of swabs used and the time spent in mopping up blood or liquid.

The main reason for the wide usage of gauze in surgery appears to be a combination of cheapness and tradition Furthermore, this must be one of very few areas of surgical practice which has not been subjected to recent research. However, different materials designed specially for the surgeons' requirements should be well within the capacity of modern textile techniques. Calcium alginate is strong enough to be used as an aid to retraction and grips the tissues well. As a result surgeons were pleased with the handling characteristics of the alginate swab. They all claimed to avoid excessive use of diathermy and therefore there was minimal change to their operative technique. Areas where the alginate swabs were thought to be of particular benefit were wound edges, the gall bladder bed and mastectomy flaps. The only adverse comment was that when the swabs were soaked through with blood they tended to matt together and had to be discarded. The alginate swab is absorbent and is itself absorbable whereas strands of gauze left behind may contribute to adhesion formation There were no side effects attributable to calcium alginate in this clinical trial and indeed they would seem unlikely, as alginates are commonly incorporated into foodstuffs such as ice cream[4] and have even been used as plasma expanders[5].

Surgical applications for alginates were suggested many years ago with the first published reports on haemostasis dating from 1947[6]. It is not clear why they never gained wide acceptance then, but the development of new textile technology, with wet spinning, improved the manufacture of alginate fibres and the quality of resulting textiles[7]. Currently, calcium alginates have been used predominantly for wound dressings[8–10], but we believe they may have much wider applications throughout surgery. The product would need to be produced cheaply, which in this case should not be a major problem as calcium alginate may be economically extracted from a variety of seaweed which may potentially be harvested at a cost less than that for cotton.

Other currently available haemostatic agents may also be considered in swab manufacture. Powders such as microcrystalline collagen are effective haemostats but could only be added to or processed into a textile swab[11]. Macrofibrillary collagen is also a more effective haemostat than some of the traditional materials such as oxidized cellulose or gelatin products, but is not absorbent. In an animal model, collagen sheets produced a granulomatous foreign body reaction and were less effective in controlling bleeding from a liver laceration than calcium alginate[3,12]. Gelatin sponge acts as a haemostat by contact activation and dissolves quickly on contact with blood[12]. Oxidized cellulose is poorly absorbent, is a weak haemostat and is more expensive than calcium alginate[11,13,14]. An alternative might be the use of gauze swabs soaked in dilute solutions of calcium, adrenaline or thrombin to reduce operative blood loss, but the logistic problems of carefully soaking each swab before use would make this impractical and associated with the risk of error in dosage. Calcium alginate swabs are absorbent, strong enough to use in retraction of tissues and, in this study, improved haemostasis. If these results are confirmed in larger studies, particularly of more major surgery where blood transfusion is routine, calcium alginate swabs have the potential to replace gauze swabs throughout surgical practice.

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Back pain following general anaesthesia and surgery: evaluation of risk factors and the effect of an inflatable lumbar support

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Factors that contribute to postoperative lumbar back pain and the effect of an inflatable lumbar support on the incidence of postoperative backache were examined. The study consisted of two parts, a pilot study in which mathematical models for appropriate support pressures were produced and the main study to assess the role of an inflatable lumbar support. The use of a support reduced the incidence of back pain on the first postoperative day from 46 to 21 per cent ($P=0\cdot007$). The patient's sex, height, weight, and the presence or absence of obesity were not found to be significant factors in the incidence of postoperative back pain. Previous back pain or arthritis in any joint tended to be associated with an increase in the severity and incidence of postoperative back pain. Postoperative back pain was more severe after procedures lasting more than 40 min. Early mobilization reduced the amount of back pain. In conclusion, patients benefit from the use of an inflatable lumbar support if they have previously suffered from backache or if they are to be anaesthetized for more than 40 min.

Keywords: Back pain, complications, lumbar support, spine, anaesthesia, postoperative

Lumbar backache has been shown to be a common complication of general anaesthesia and surgery[1–4]. It is thought to result from strain of the spinal ligaments when paraspinal muscle relaxation leaves the normal lumbar lordosis unsupported during anaesthesia and the spine becomes straightened against the operating table. If this hypothesis is correct, backache would be expected to occur more frequently or with greater severity when anaesthesia is prolonged or involves the use of neuromuscular blocking agents. Backache has been reported to be more likely in patients who have been operated on in the lithotomy position[1]. Patients who have pre-existing backache or a previous spinal injury might be expected to be more at risk of postoperative back pain.

O'Donovan *et al.*[2] have shown that a simple inflatable lumbar support, placed in the lumbar lordosis during anaesthesia and surgery, reduces the incidence and severity of postoperative back pain in women undergoing gynaecological or breast surgery. The present study sought to evaluate the risk factors for postoperative backache and the extent to which it is influenced by use of a lumbar support. The study consisted of a pilot study followed by the main study.

Patients and methods

Pilot study

The pilot study was designed to determine the pressure to which a lumbar support should be inflated in individual patients. An inflatable lumbar support was used as described by Carrie[5]. This consisted of an empty 3-litre urological irrigation solution bag (Travenol Laboratories, Thetford, UK) connected to a sphygmomanometer bulb and an anaeroid gauge or mercury column.

Twelve male and 12 female volunteers, without a previous history of back pain and aged from 19 to 52 years, were studied. Each volunteer lay in turn in lithotomy and supine positions on each of two types of operating table. One table type (Stille Werner (UK) Ltd., Woking, UK) has a deep, relatively soft mattress and the other (Eschmann Bros and Walsh Ltd., Lancing, UK) has a thinner, firm, corrugated mattress. These were respectively designated soft and hard tables. Each volunteer was also studied, in the supine position, on a trolley of the type used to transfer patients to and from the operating room, and on which, in some operating rooms, anaesthesia is induced. This trolley has a soft, thin mattress. For each surface and position, the inflatable support was placed under the lumbar spine of the subject and inflated stepwise by increments of 2 mmHg. Inflation was continued until the subject stated that it was no longer comfortable. The preceding pressure reading was then designated the maximum comfort pressure (MCP) and the mean of three such readings was designated the mean maximum comfort pressure (MMCP). The heights and weights of all subjects were recorded. The order in which MMCP was measured for different surfaces and positions was varied between subjects.

A series of mathematical models was fitted to the MMCP data by the method of maximum likelihood[6] using the GLIM (generalized linear interactive modelling system, Numerical Algorithms Group, Oxford, UK) 3.77 computer package[7]. The MMCPs were found to be positively skewed with a log-normal distribution; they were converted to natural logarithms before analysis. Separate analyses were carried out for each surface/position combination.

The subject's height and weight, but not age, were found to correlate with MMCP for a given surface/position. Interestingly, MMCP was found to be positively correlated with height in male subjects, but negatively so in female subjects. The individual correlations of MMCP with height and weight, and the equations relating log MMCP to sex, height, weight, surface and position are shown in *Tables 1* and *2*. The equations in *Table 2* account for approximately 70 per cent of the variability in MMCP between subjects of the same sex and the same surface/position. MMCP was poorly correlated for a given subject between different surfaces, but MMCP in the lithotomy position was linearly related to MMCP in the supine position on the same surface ($P=0\cdot05$).

It was observed that at inflation pressures greater than 40 mmHg the support became excessively distended and lifted some subjects from the table. It was decided that 40 mmHg would be the maximum inflation pressure used during the main study.

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Table 1 *Pilot study: variation of MMCP with sex, position and surface; correlation with subject height and weight*

	Mean (s.d.) MMCP (mmHg)	Pearson correlation			
		Height/MMCP	*P*	Weight/MMCP	*P*
Men					
Trolley, supine	21·2(6·5)	0·384	0·217	0·330	0·296
Soft table					
Supine	24·7(10·8)	0·660	0·020	0·321	0·308
Lithotomy	35·1(17·0)	0·687	0·014	0·596	0·041
Hard table					
Supine	19·8(3·6)	0·479	0·115	0·394	0·296
Lithotomy	30·7(8·7)	0·168	0·603	0·256	0·422
Women					
Trolley, supine	15·9(8·3)	−0·486	0·109	0·228	0·475
Soft table					
Supine	16·3(6·3)	−0·497	0·100	0·273	0·392
Lithotomy	24·3(7·8)	−0·445	0·147	0·288	0·363
Hard table					
Supine	17·2(4·3)	−0·606	0·037	0·100	0·758
Lithotomy	30·7(8·7)	−0·568	0·054	0·217	0·499

MMCP, mean maximum comfort pressure

Table 2 *Relation between subject height and weight, table type, and MMCP*

Soft table, supine position	
Men	Log MMCP = −2·763 + 0·03712ht − 0·01057wt
Women	Log MMCP = 16·067 − 0·10738ht + 0·06523wt
Soft table, lithotomy position	
Men	Log MMCP = −1·203 + 0·02366ht + 0·007107wt
Women	Log MMCP = 13·787 + 0·08674ht + 0·054751wt
Hard table, supine position	
Men	Log MMCP = 1·432 + 0·0009904ht + 0·02084wt
Women	Log MMCP = 12·302 − 0·0657ht + 0·02084wt
Hard table, lithotomy position*	
Men	Log MMCP = 3·139 − 0·001171ht + 0·006828wt
Women	Log MMCP = 14·909 − 0·09196ht + 0·051698wt

* MMCP on hard table, lithotomy position, is derived from measured $\text{MMCP}_{\text{supine}}$ on same surface: $\log \text{MMCP}_{\text{lithotomy}} = 1{\cdot}104 + 0{\cdot}7538 \log \text{MMCP}_{\text{supine}}$; MMCP, mean maximum comfort pressure; ht, height (cm); wt, weight (kg)

Main study

In all, 114 adult patients undergoing elective surgery in either the supine or lithotomy positions were studied. Patients excluded from the study included day-stay patients, obstetric patients and patients having orthopaedic procedures to the back, hip or lower limb. All patients gave their informed consent to participate in the study. At a preoperative visit, patient's height and weight were recorded, as well as any history of back pain or injury, or of arthritis. The presence of obesity was noted.

In some operating rooms the practice was to anaesthetize patients on the operating table whilst in others induction was performed on a trolley and the patient was transferred to the table after induction. When patients were anaesthetized on the table, a MMCP in the supine position was measured for each patient before induction of anaesthesia. The inflatable support was placed beneath the lumbar curve and three MCP readings were obtained exactly as in the pilot study. If the patient was then to be placed on the operating table in the lithotomy position, the MMCP in lithotomy was calculated from the measured MMCP supine according to the relation derived in the pilot study. In those operating rooms in which patients were anaesthetized on a trolley, the formulae derived from the pilot study were used to calculate MMCP from the patient's height and weight in the supine or lithotomy positions as appropriate.

The lumbar support was placed, deflated, under all subjects before induction of anaesthesia. Whether it was to be inflated or not was decided by reference to computer-generated randomization lists. If the support was to be inflated, this was done rapidly as soon as the patient's eyelash reflex was lost. The support was inflated to the measured or calculated MMCP (subject to a maximum inflation pressure of 40 mmHg) for the appropriate surface and position, and maintained at that pressure throughout the operation. It was deflated immediately before lifting the patient from the table at the end of the procedure. Patients thus remained unaware of whether the support had been inflated or not.

The anaesthetic technique to be used was at the discretion of the anaesthetist. The duration of anaesthesia, the operating position and the use of depolarizing or non-depolarizing muscle relaxants were recorded.

Patients were visited on the first day after operation. They were asked whether they had backache, and whether it was mild, moderate or severe. The degree of postoperative pain was noted using the same scale, and the type of analgesia received during the preceding 4 h was recorded. Analgesia was classified as none, simple analgesics, weak opioids (excluding buprenorphine) or strong opioids. It was noted whether the patient had received buprenorphine in the previous 12 h.

Each patient was handed a simple questionnaire which they were asked to complete and return on the 14th day after operation. This asked whether back pain had occurred at any time during the 13 days after the first postoperative day and, if so, how long it had lasted and how severe had it been.

Statistical analysis

Patients were first grouped according to whether or not the inflatable support had been inflated – supported and unsupported groups. The first analysis compared these two groups separately for each recorded variable. The analysis was repeated, first with the patients grouped according to the backache they experienced on the first day after operation and, second, according to the backache they reported up to, and including, the 14th day after operation. On both days patients were grouped initially by the presence or the absence of backache, and then by its severity.

Continuous variables were analysed using Student's unpaired *t* test or a one-way analysis of variance. Durations of operation were found to have a positively skewed distribution, so they were converted to natural logarithms for analysis. All other continuous variables were found to have approximately normal distributions, and were analysed untransformed.

Categorical variables were examined by contingency table (χ^2) using Yates' correction where appropriate.

To examine the relative importance of measured variables on the incidence and severity of backache, a series of multivariate analyses was performed at both day 1 and day 14 after operation. For the incidence data, multiple logistic regression analyses were performed[8]. For the severity data, ordinary multiple regression analyses were used. In both types of analysis, regression equations were developed in a forward, stepwise manner to give the best combination of independent variables for predicting the incidence and severity of backache for an individual patient. Computations were performed using the Statistical

Package for the Social Sciences (SPSS)[9] and GLIM 3.77[7] computer packages Statistical significance has been set at the conventional 5 per cent level, although some differences significant at the 10 per cent level have been reported as indicating trends

Results

Comparison of supported and unsupported groups

In the 114 patients studied, the lumbar support was inflated during operation in 58 (51 per cent) cases and was not inflated in 56 (49 per cent) cases. There were no significant differences in mean age, height or weight between the groups (*Table 3*). The reporting of previous backache, back injury or arthritis was similar, as was the distribution of type of operation, position on the operating table and the use of muscle relaxants.

On the first day after operation, 12 (21 per cent) of the patients in the supported group reported lumbar backache, whereas 26 (46 per cent) of the patients in the unsupported group experienced backache ($P = 0{\cdot}007$). The reporting of postoperative pain and the use of analgesics was similar (*Table 4*) Where backache occurred, there was no significant difference in its severity between the two groups

Table 5 shows the interaction of a history of back pain with the effect of the lumbar support. If the spine is unsupported during surgery, previous backache sufferers have a 56 per cent chance of experiencing backache on the first day after operation, whereas patients with no such history have a lower chance of 38 per cent. However, if the lumbar support is inflated, the risk is similar at 22 and 20 per cent respectively. *Table 6* shows the interaction of support inflation with the duration of procedure. The support has no significant effect if the duration of procedure is less than 40 min, but becomes significant ($P = 0{\cdot}004$) where the duration of anaesthesia is 40 min or more.

Eight-five (75 per cent) patients returned the 14-day postoperative questionnaire. Of these 37 (44 per cent) were in the supported group and 48 (56 per cent) were in the unsupported group. Sixteen (43 per cent) of the supported group patients and 18 (38 per cent) of the unsupported group patients reported having had backache at some time in the 14-day period after operation. The results suggested that backache might occur earlier in the unsupported patients (mean 2·2 days) than in the supported group (mean 3·4 days) ($P = 0{\cdot}08$). The mean duration of reported backache episodes was 6 days, and this was not affected by inflation of the support.

Table 3 *Characteristics of 114 patients in supported and unsupported groups*

Factor	Supported group	Unsupported group
Number	58(51)	56(49)
Mean(s.d.) age in years	48(17·7)	47·0(18·4)
Mean(s.d.) height in cm	168·3(9·0)	163·4(16·1)
Mean(s.d.) weight in kg	65·97(10·44)	65·23(13·01)
Sex		
Males	28(48)	20(36)
Females	30(52)	36(64)
Previous backache		
No	40(69)	29(52)
Yes	18(31)	27(48)
Arthritis		
No	47(81)	39(70)
Yes	11(19)	17(30)
Previous back injury		
No	49(84)	51(91)
Yes	9(16)	5(9)
Types of procedure		
Abdominal	31(53)	28(50)
Head and neck	8(14)	9(16)
Body wall	12(21)	11(20)
Transurethral, vaginal, perineal	7(12)	8(14)
Position		
Supine	43(74)	45(80)
Lithotomy	15(26)	11(20)
Suxamethonium used		
Yes	20(34)	19(34)
No	38(66)	37(66)
Non-depolarizing relaxant used		
Yes	49(84)	47(84)
No	9(16)	9(16)

Values in parentheses are percentages, unless otherwise stated

Table 4 *Patients in supported and unsupported groups. incidence and severity of backache, pain reported on first postoperative day and analgesia requirements*

	Support inflated ($n = 58$)	Support not inflated ($n = 56$)
Backache		
No backache	46(79)	30(54)
Backache	12(21)	26(46)*
Mild	6(10)	13(23)
Moderate	4(7)	7(13)
Severe	2(3)	6(11)
Pain at operation site		
None	17(29)	18(32)
Mild	22(38)	19(34)
Moderate	12(21)	12(21)
Severe	7(12)	7(13)
Analgesics received in previous 4 h		
None	35(60)	35(63)
Simple	7(12)	5(9)
Weak opioid	7(12)	1(2)
Strong opioid	9(16)	15(27)
Buprenorphine in previous 12 h	4(7)	0

Values in parentheses are percentages; * $P = 0{\cdot}007$

Table 5 *Interaction of history of previous backache and support inflation on the incidence of first-day backache*

Previous backache	Support inflated	n	No. with backache
No	No	29	11(38)
	Yes	40	8(20)
Yes	No	27	15(56)
	Yes	18	4(22)

Values in parentheses are percentages

Table 6 *Interaction of the effects of support inflation and duration of anaesthesia on the incidence of first-day backache*

Duration of anaesthesia	Support inflated	n	No. with backache	P
<40 min	No	14	4(29)	
	Yes	13	3(23)	n.s.
≥40 min	No	42	22(52)	
	Yes	45	9(20)	0·004

Values in parentheses are percentages, n.s., not significant

Analysis of variables related to the incidence and severity of postoperative backache

Measured variables that had a significant effect on the incidence of first-day backache were detected by multiple logistical regression analysis (*Table 7*). The effect of inflating the lumbar support in reducing the incidence of backache is confirmed ($P = 0{\cdot}007$). The table type also had a significant effect. patients who were operated on on the soft table had a lower incidence of first-day backache ($P = 0{\cdot}007$).

Table 7 *Patients grouped according to the presence or absence of backache on the first postoperative day, factors found to influence the incidence of backache by multiple logistic regression analysis*

	No. with backache (n=38)	No without backache (n=76)	P
Lumbar support			
Inflated	12(32)	46(61)	
Not inflated	26(68)	30(39)	0·007
Table type			
Hard	14(37)	10(13)	
Soft	24(63)	66(87)	0·007
Duration of anaesthesia			
⩾40 min	31(82)	56(74)	
<40 min	7(18)	20(26)	n.s.
Position			
Supine	26(68)	62(82)	
Lithotomy	12(32)	14(18)	n.s.
Previous back pain			
Yes	19(50)	26(34)	
No	19(50)	50(66)	0·155
History of arthritis			
Yes	14(37)	14(18)	
No	24(63)	62(82)	0·055
Analgesia received in previous 4 h			
None	23(61)	47(62)	
Simple	4(11)	8(11)	
Weak opioid	1(3)	7(9)	
Strong opioid	10(26)	14(18)	n.s.
Received buprenorphine in previous 12 h	0	4(5)	n.s.
Pain at operation site*			
None	17(45)	18(24)	
Mild	8(21)	33(43)	
Moderate	7(18)	17(22)	
Severe	6(16)	8(11)	n.s.

Values in parentheses are percentages; * pain at operation site and analgesia are included for comparison, n.s., not significant

Table 8 *Multivariate analysis of the incidence of backache at day 1 after operation*

	Coefficients	Standard error	r_2 (%)
Constant	0·574	0·470	—
Support inflated (yes)	−1·031	0·444	6·0
Table type (soft)	−1·434	0·511	10·4
Arthritis present (yes)	−1·069	0·486	13·8

There were possible relations between a previous history of back pain or arthritis (in any joint) and postoperative back pain but these failed to achieve statistical significance. There was no relation between obesity, operating position or the use of relaxants and the occurrence of first-day backache. There was a similar usage of analgesics in those who did and did not have backache.

The technique of multivariate analysis was used to assess the relative importance of the variables related to first-day backache. This confirmed that the most important such variable was inflation or otherwise of the support, followed by table type and a history of arthritis (*Table 8*).

The influence of variables on the severity of backache was assessed by multiple regression analysis (*Table 9*). No moderate or severe backache occurred in patients having procedures shorter than 40 min, whereas this occurred in 13 and 9 per cent respectively of patients having longer procedures ($P=0·045$). There was no significant relation between table type and backache severity. Patients operated on in the lithotomy position had more severe backache, but this difference did not attain significance ($P=0·072$).

The above analyses were then repeated in respect of backache occurring at any time up to 14 days after operation. Backache incidence and severity increased with duration of anaesthesia ($P=0·063$ and $P=0·032$ respectively). A previous history of arthritis was associated with increased incidence and severity of postoperative backache ($P=0·032$ and $P=0·029$). Patients who had mobilized by the first day after operation were less likely to experience subsequent backache ($P=0·022$), and their backache, if it occurred, was less severe ($P=0·005$).

Inflation of the support did not significantly alter the backache incidence over the following 2 weeks, nor did a previous history of back pain.

Discussion

Back pain as a complication of anaesthesia was mentioned in a review by Sir Ivan Magill in 1937[3]. He attributed it to the 'stretching of lumbar and sacral ligaments' and stated: 'The lumbar convexity should be suitably supported when the patient is on the operating table'. The problem was next mentioned by Schleyer-Saunders[4] who also attributed postoperative back pain to intraoperative stretching of spinal ligaments and wrote that this was aggravated by 'extreme lithotomy position'. Brown and Elman[1] found that postoperative back pain occurred in 19 per cent of patients after general anaesthesia, with the risk being slightly higher for those operated on in the lithotomy position. In their study, the proportion of patients developing backache increased with the duration of anaesthesia. O'Donovan *et al.*[2] have demonstrated the efficiency of an inflatable lumbar support in women undergoing gynaecological or breast surgery.

Our results confirm the beneficial effect of the support in patients of both sexes, and in other types of surgery. The overall incidence of first-day back pain was reduced from 46 per cent in the unsupported group to 21 per cent in the supported group. Reported degrees of postoperative pain and analgesic use were similar between the groups. Differences in pain perception or analgesic state did not influence the reporting of back pain. Patients with a previous history of back pain appear more likely to benefit from use of a support, as do those who will be anaesthetized for 40 min or longer.

In the previous study by O'Donovan *et al.*[2] only two inflation pressures were used in the lumbar support: 25 mmHg for supine patients and 30 mmHg for those in the lithotomy

Table 9 *Patients grouped by severity of backache on the first postoperative day, factors found to influence backache severity by multiple regression analysis*

	Backache severity				
Factor	None	Mild	Moderate	Severe	P
Support inflated					
Yes (n=58)	46(79)	6(10)	4(7)	2(3)	
No (n=56)	30(54)	13(23)	7(12)	6(11)	n.s.
Duration of anaesthesia					
<40 min (n=27)	20(74)	7(26)	0	0	
⩾40 min (n=87)	56(64)	12(14)	11(13)	8(9)	0·045
Type of table					
Hard (n=24)	10(42)	9(37)	3(13)	2(8)	
Soft (n=90)	66(73)	10(11)	8(9)	6(7)	n.s.
Position					
Supine (n=88)	62(70)	11(13)	10(11)	5(6)	
Lithotomy (n=26)	14(54)	8(31)	1(4)	3(12)	0·072

Values in parentheses are percentages; n.s., not significant position. Following the findings of our pilot study, we elected to use an individually measured or calculated pressure within the support We believe this to be logical in view of the very wide between-subject variability of MMCP and the fact that correlations with height and weight accounted for a large part of this variability. We, like O'Donovan *et al.*, made the assumptions that MMCP in the awake patient is the appropriate pressure to use in the anaesthetized patient and that this degree of lumbar support is the most likely to reduce postoperative back pain.

It would be convenient to use a fixed contour support rather than an inflatable bag. The wide range of comfort pressures obtained in the pilot study presumably reflects differences in patient's lumbar lordosis. A number of differently shaped supports might be required.

When the patients were grouped by the presence or absence of backache at day 1, it was possible to assess the importance of other risk factors in the aetiology of back pain, although inflation or not of the support remained the most important factor. The influence of operative duration, as reported previously[4], was confirmed, although in the present study an increased duration of procedure was more important in increasing the severity of first-day back pain than its incidence. First-day back pain is less likely to occur when the operation is performed on the softer of the two table types. We postulate that the mattress on this table is just sufficiently conformable to provide some support for the lumbar region The presence of obesity and the use of muscle relaxants were not found to be significant factors in the pathogenesis of postoperative backache.

The risk of postoperative backache might be expected to increase when the procedure is performed with the patient in the lithotomy position since anterior rotation of the pelvis may contribute to spinal ligamentous stretch[10]. The results suggest an increase in the risk of backache in patients who were in the lithotomy position but this did not attain statistical significance.

The finding that a previous history of back pain was important in influencing the incidence and severity of postoperative back pain was expected, but these trends did not attain statistical significance and were recorded only on the first day after operation. The influence of a history of arthritis was not significant on day 1, although it was on day 14. The same applied whether a patient had mobilized or not at day 1. These factors are thus more important in influencing back pain which appears after the first postoperative day.

In summary, this study confirms that postoperative backache occurs in a high proportion of patients after general anaesthesia, and that its incidence and severity are increased after long procedures and when surgery is performed on a hard table surface. A lumbar support is simple and safe to use, and substantially reduces the proportion of patients suffering from postoperative back pain. Patients are particularly likely to benefit from use of the support if they have previously suffered from backache or if they are to be under anaesthesia for longer than 40 min.

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Changes in cardiorespiratory and muscle function associated with the development of postoperative fatigue

An understanding of the factors which contribute to postoperative fatigue may benefit the rehabilitation of patients after surgery. Subjective feelings of fatigue and fatigue measured objectively in the adductor pollicis muscle after ulnar nerve stimulation have been studied in relation to changes in cardiorespiratory function and muscular efficiency both at rest and when walking on a treadmill at a work rate of 20 and 56 kpm min^{-1}. Twelve patients admitted for elective abdominal surgery were studied before operation and again on the third postoperative day. The postoperative period was characterized by an increased feeling of fatigue. Surgery had no effect upon fatigue in the adductor pollicis muscle suggesting that the genesis of postoperative fatigue is partly central in origin. Muscular efficiency(s.d.) fell from 34(6) per cent before operation to 22(3) per cent ($P<0.05$) *on the third postoperative day and was accompanied by a 19 per cent rise in the net energy(s.d.) expenditure (7·3(0·8) to 8·6(0·3) kJ min^{-1};* $P<0.03$) *required to perform a given workload. The increased cardiorespiratory effort and reduced muscular efficiency associated with the performance of low-intensity exercise may limit mobilization after surgery and contribute to a greater feeling of fatigue.*

Keywords: Fatigue, postoperative care, spirometry, exercise test

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Convalescence after surgery in man is characterized by a period of fatigue the duration of which is unrelated to the magnitude of the surgery[1]. Recent studies, in which a fatigue scale model was applied to patients after abdominal surgery, have shown that one-third developed a feeling of tiredness which was sustained throughout the first postoperative month and the remainder returned to preoperative levels of fitness 3–4 weeks after operation[2].

Despite the frequency with which postoperative patients suffer fatigue relatively little is known about the underlying mechanisms. An editorial in *The Lancet*[3] lamented the paucity of information and concluded: 'until postoperative fatigue has been properly defined and better ways are found to measure it, our almost total ignorance of this important matter will continue to be a trial to surgical patients and a nagging concern to their doctors'. One reason for this lack of knowledge is that previous studies have attempted to relate purely subjective feelings of tiredness to standard physiological stress tests such as cycle ergometry[2,4–6]. The use of tests such as these delays investigation until patients are convalescent, by which time changes in factors such as cardiorespiratory function and muscular efficiency, which might contribute to postoperative fatigue, may no longer be evident. With these limitations in mind, and aware of the need for early postoperative mobilization, we have successfully applied a treadmill test to a group of patients who had undergone elective abdominal surgery 3 days previously[7]. The aim of this study was to use the treadmill test to examine the influence of surgery upon cardiorespiratory function and muscular efficiency and to relate such changes to objective and subjective assessments of fatigue.

Patients and methods

Patients

The study was limited to patients admitted for elective abdominal procedures. Preoperative screening for cardiorespiratory and vascular disease was performed in all cases and consisted of clinical examination, pulmonary function tests and electrocardiograph. Patients with limited exercise tolerance, angina, intermittent claudication, or alterations in thyroid status were excluded from the study, as were those taking β-blockers or steroids. All measurements were performed before the evening meal and patients were able to eat according to the usual protocol for preoperative preparation or postoperative condition.

Methods

Measurements were made of analogue fatigue score, objective muscle fatigue and cardiorespiratory function before operation and again on the third postoperative day.

Analogue fatigue score. A subjective assessment of fatigue was obtained using the fatigue scale model of Christensen *et al.*[2]. Based on an analogue scale of 1–10 the patient scores himself 1 when considered fit (tired only by violent exertion, normal need of sleep), and 10 when fatigued (unable to cope with daily chores or short walks, pronounced need for sleep). The fatigue scale was explained to the patient at each test, but scored by the patient alone without information or discussion of previous values.

Skeletal muscle function. Objective measurements of fatigue were made in the adductor pollicis muscle of the thumb as described previously[8]. The ulnar nerve was stimulated at 20 Hz for 1 s and the maximal relaxation rate obtained. The patient was then asked to make a maximal voluntary contraction for 30 s followed by a further stimulated contraction at 20 Hz for 1 s. Muscle fatigue was defined as the percentage reduction in maximal relaxation rate following a sustained maximal voluntary contraction.

Exercise test. Exercise tests were performed on a Powerjog EG30® treadmill (Sports Engineering Ltd., Birmingham, UK) and measurements of respiratory gas exchange, breathing patterns and heart rate made with an Oxycon 4 Ergo-spirometer® (Mijnhardt B.V., Bunik, Holland). Patients were measured at rest and then at a workload of 20 and 56 kpm min^{-1}, this value being chosen from a previous study[7] as suitable for postoperative patients. The required workload was obtained at a treadmill speed of 1 km h^{-1} by variation in the gradient from

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Table 1

Patient details	
n	12
Age range (years)	27–78
Median (years)	46
Sex	6 men, 6 women
Types of operation	Cholecystectomy, 6 Abdominal gastrectomy, 3 Peptic ulcer surgery, 3

2–5 per cent No recordings were taken at the initial test which was simply to acclimatize the patient to his or her surroundings and to the apparatus.

Tests were performed in a clinical laboratory with a member of the medical staff (M.R.Z) in constant attendance and full resuscitation facilities available The electrocardiograph was monitored throughout the test and recovery period. Patients were asked to exercise on the treadmill, without holding the safety rail, for a period of 4 min at each work rate, at which time a steady state was assumed[9]. All recordings were taken during the final minute of the test.

Calculations

Work rate[10].

$$W = (S \times G \times BW)/60$$

where W = work rate (kpm min^{-1}), S = treadmill speed (m h^{-1}),
G = gradient (%), BW = body weight (kg)

Energy expenditure[11].

$$EE = 4\,18[3\,941(V_{O_2}) + 1\,106(V_{CO_2})]$$

where EE = energy expenditure (kJ min^{-1})
V_{O_2} = oxygen consumption (l min^{-1})
V_{CO_2} = carbon dioxide production (l min^{-1})
4 18 kJ = 1 kcal

Muscular efficiency. For the calculation of muscular efficiency patients were exercised at work rates of 20 kpm min^{-1} and 56 kpm min^{-1}, energy expenditure being measured at each work rate. Muscular efficiency has been defined as the ratio of the net change in work rate divided by the net change in energy expenditure[12]

$$\Delta \text{ efficiency } (\%) = \frac{\Delta W}{\Delta EE} \times 100$$

where ΔW = calorie equivalent of increment in work performed above previous work rate
ΔEE = increment in calorie output above that at previous work rate
1 kpm min^{-1} = 0 0025 kcal min^{-1}

Reproducibility

For three patients with gastrointestinal malignancy studied serially over 5 days the coefficient of variation for measurements of resting oxygen consumption was 9 per cent and carbon dioxide production 6 per cent When walking on a treadmill at a speed of 1 km h^{-1} with a gradient of 2 per cent the coefficient of variation was 10 per cent for oxygen consumption and 12 per cent for carbon dioxide production. When repeating the same exercise load after a 10 min rest the coefficient of variation for oxygen consumption was 2 per cent and for carbon dioxide production 4 per cent

Postoperative management

Pain control. No patients were receiving analgesia at the time of the preoperative test. In two patients thoracic epidurals were inserted before the commencement of surgery and fentanyl administered by syringe pump at a rate of 60 g h^{-1}. The normal routine for postoperative care dictated that all epidural cannulae were removed on the morning of the third postoperative day All infusions had therefore been withdrawn for at least 6 h before testing. Patients not restored to an oral intake received sublingual buprenorphine (Temgesic, Reckitt and Colman, Hull, UK) whereas all others were maintained on oral diclofenac or paracetamol No medication was provided for at least 2 h before the study.

Fluid and electrolytes All patients were provided with a standardized fluid regimen comprising 1000 ml of 0 9 per cent saline .2000 ml 5 per cent dextrose at a rate of 2500–3000 ml 24 h^{-1}. No patient received parenteral nutrition over the study period.

Statistical methods

Data are expressed as mean(s.e.m.) Statistical significance was determined using the Wilcoxon signed rank test for paired data, and the Mann–Whitney *U* test for unpaired data A level of significance of $P < 0\,05$ was used throughout the study.

Ethical considerations

The study was approved by the research ethics committee of the Northern General Hospital and after detailed explanation consent was obtained from all patients.

Results

Fourteen patients admitted for elective abdominal surgery were studied. Two patients who had completed the preoperative study developed postoperative complications (respiratory failure, 1; multiple ventricular ectopics, 1) which prevented further study. Details of these patients have been excluded from analysis. All other patients were able to complete the protocol and their details are shown in *Table 1*.

Postoperative fatigue

Of the 12 patients 11 reported an increased feeling of tiredness after operation (*Figure 1*). Using the analogue fatigue score there was a rise in the subjective feeling of fatigue from a mean(s.e.m.) of 2·6(0 3) arbitrary units before operation to 7·0(0·5) arbitrary units on the third postoperative day ($P < 0{\cdot}01$). Although the majority of patients had an increased perception of fatigue, objective measurement of skeletal muscle function as measured in the adductor pollicis muscle was unchanged by surgery (*Figure 1*).

Respiratory gas exchange

Measurements of respiratory gas exchange were made at rest and during the exercise and recovery periods. Steady state conditions were reached 3 min after the commencement of exercise, the time taken to achieve this state being unaltered by surgery (*Figure 2*). Resting values and those during the final minute of exercise are shown in *Table 2*. Surgery had little influence upon oxygen consumption (V_{O_2}) or carbon dioxide production (V_{CO_2}) at rest. Although the V_{O_2} for walking was significantly higher than at rest ($P < 0\,01$) there was no significant difference between the pre- and postoperative values

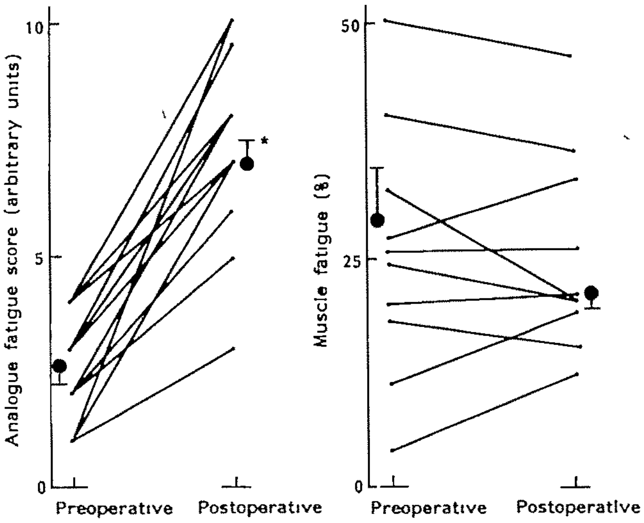

Figure 1 *Effect of surgery on analogue fatigue score and fatigue in adductor pollicis muscle Mean(s e m.);* * $P < 0\,01$

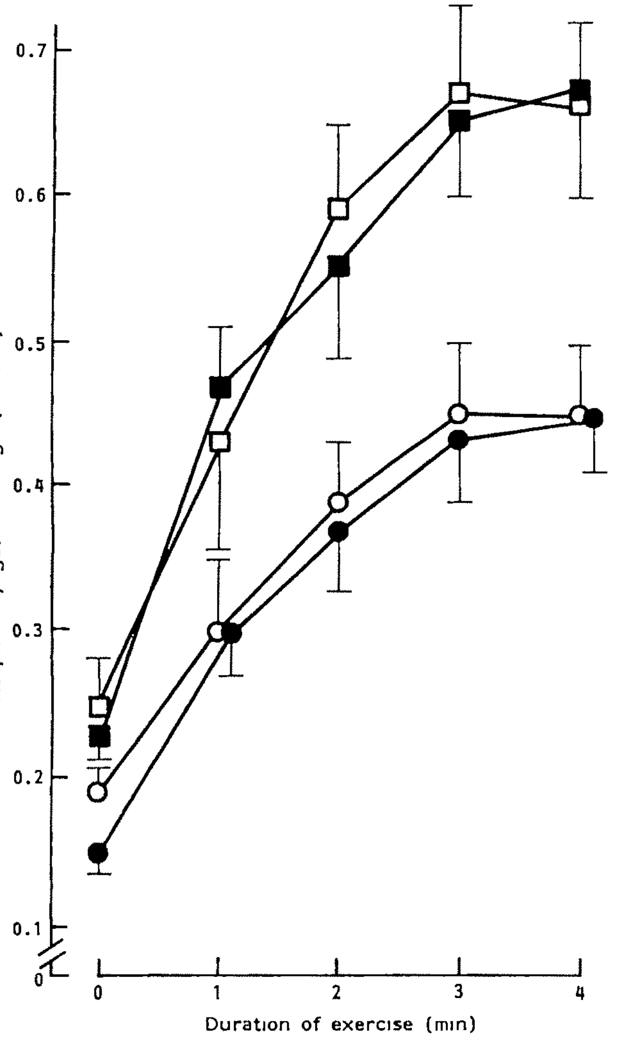

Figure 2 *Effect of low intensity exercise upon respiratory gas exchange.* ○ = V_{O_2}, *preoperative;* ● = V_{O_2}, *postoperative,* □ = V_{CO_2}, *preoperative;* ■ = V_{CO_2} *postoperative At rest at zero minutes*

(0·61(0·05) *versus* 0·66(0·04) l min^{-1}) which suggests that surgery had little influence upon respiratory gas exchange.

Breathing patterns

The respiratory demands for exercise were met by a rise in minute ventilation (V_e) from 7·1(0·9) to 14·5(1·8) l min^{-1} before operation and 7·4(0·9) to 16·4(2·0) l min^{-1} after operation. Allowing for changes in resting V_e the net difference between the pre- and postoperative responses amounted to 22 per cent ($P = 0·07$) The increase in V_e was associated with equal rises in respiratory rate (F_r) and tidal volume (V_t), the changes being similar before and after surgery (*Table 2*).

Heart rate

Resting heart rate was significantly higher after operation (75(3) to 86(4) beats min^{-1}; $P < 0·05$) Similarly the heart rate obtained during the final minute of exercise was increased from a preoperative rate of 87(4) beats min^{-1} to 103(5) beats min^{-1} after surgery ($P < 0·01$).

Muscular efficiency

Before operation patients undertook incremental workloads of 20 kpm min^{-1} and 56 kpm min^{-1} with a muscular efficiency of 34(6) per cent. When these workloads were repeated on the third postoperative day the muscular efficiency had fallen to 22(3) per cent ($P < 0·05$).

Discussion

Although subjective feelings of fatigue were increased in 11 of the 12 patients studied (*Figure 1*), measurements of adductor pollicis function failed to show any significant change in muscle fatigue after surgery. For reasons of patient compliance we measured fatigue in relation to changes in muscle relaxation rate before and after a 30 s maximal voluntary contraction rather than the more conventional and somewhat unpleasant method of measuring force loss during a stimulated contraction at 20 Hz for 30 s (Reference 13). In spite of such differences our results are similar to those of Brough *et al.*[13]. This suggests that the genesis of postoperative fatigue is mediated, at least in part, by mechanisms which act centrally.

Subjective factors such as pain and motivation may be important influences on fatigue but are difficult to measure and existing indices of psychomotor performance are of limited use in the postoperative period[14]. Pain may be involved in the genesis of fatigue by reducing the feeling of well-being and contributing to the increased respiratory effort required for ventilation. The majority of patients received intramuscular opiates in the immediate postoperative period and by the time of the study had been started on sublingual or oral medication. Although epidural fentanyl was administered to two patients, epidural catheters were removed at least 6 h before testing. Opiates are known to depress respiration, the duration of effect of epidural fentanyl is under 2 h (Reference 15) and it is therefore unlikely that respiratory gas exchange would be influenced. Patients were able to respond to the requirements of the postoperative exercise test by an increase in tidal volume, a feature unlikely to be associated with significant abdominal wound pain. It would appear, therefore, that by the third postoperative day pain was not a limiting factor for the exercise test.

Changes in the amount of work accomplished for a given energy expenditure might contribute to the feeling of fatigue. Unfortunately calculation of muscular efficiency at low intensity workloads tends to underestimate the true value since a high proportion of energy is expended in overcoming elastic and viscous resistances; unmeasured work which Hesser *et al.*[16] have calculated may account for over 30 per cent of V_{O_2}. Because of the limitations of net efficiency calculations at low work intensities, Gaesser and Brooks[12] have suggested that the delta efficiency calculation represents the most accurate estimate of muscular efficiency, each increment in caloric expenditure being assumed to represent the additional V_{O_2} of only the working muscles. Before operation delta efficiency was cal-

Table 2 *Effect of surgery and exercise upon cardiorespiratory function and muscular efficiency*

	Before operation		After operation	
	Rest	Exercise	Rest	Exercise
Oxygen consumption, V_{O_2} (l min^{-1})	0·25 (0·03)	0·61 (0·05)	0·23 (0·02)	0·66 (0·04)
Carbon dioxide production, V_{CO_2} (l min^{-1})	0·18 (0·03)	0·43 (0·04)	0·15 (0·02)	0·44 (0·04)
Heart rate (beats min^{-1})	75 (3)	87 (4)	86 (4)*	103 (5)†
Minute ventilation, V_e (l min^{-1})	7·1 (0·9)	14·5 (1·8)	7·4 (0·9)	16·4 (2.0)
Respiratory rate, F_r (beats min^{-1})	14·2 (1·2)	20·0 (1·2)	17·1 (1·4)	24·8 (1·5)†
Tidal volume, V_t (l)	0·51 (0·06)	0·73 (0·09)	0·42 (0·03)	0·66 (0·07)
Delta muscular efficiency (%)	34 (6)		22 (3)*	

Results expressed as mean(s.e.m.), preoperative *versus* postoperative value, * $P < 0·05$, † $P < 0·01$

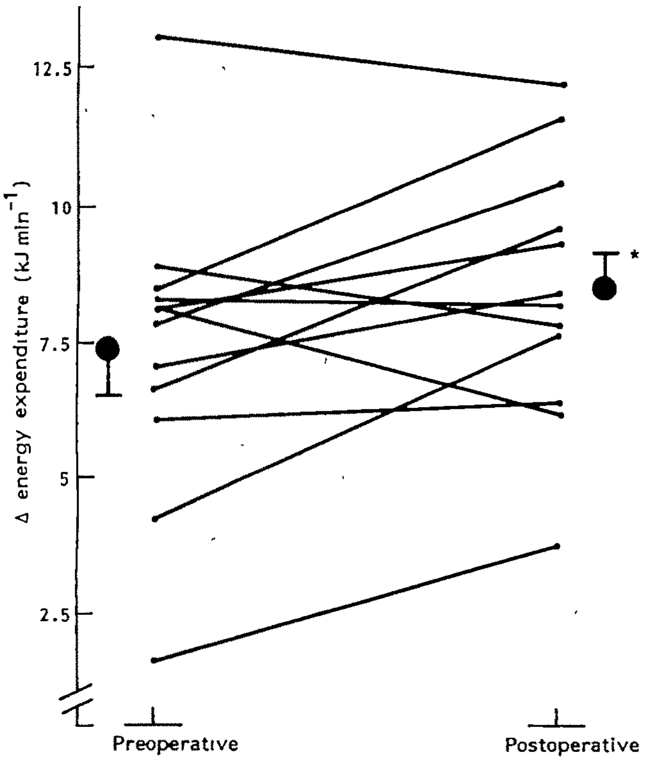

Figure 3 *Effect of surgery upon net energy expenditure (energy expenditure during exercise (AEE) − resting energy expenditure (REE)) Mean(s.e.m.);* * $P<0{\cdot}03$

culated as 34 per cent, compared with 28 per cent reported by Gaesser and Brooks[12] and 27 per cent of Goldstein *et al.*[17], both of the comparative studies being undertaken on normal subjects of younger age (range 19–30) on a bicycle ergometer. By the third postoperative day delta efficiency had fallen to 22(3) per cent ($P<0{\cdot}05$).

Mechanisms underlying reduction in muscular efficiency are uncertain. Starvation is probably not important, Poole and Hensen[18] reporting no change in work efficiency in obese patients losing weight on a calorie restricted diet. Changes in efficiency probably arise as a consequence of additional oxygen demand by respiratory and cardiac muscle increasing the oxygen consumption for any given workload.

Since the studies of Cuthbertson in the 1930s[19,20] it has been known that trauma induces a series of metabolic changes that influence resting energy expenditure (REE). In this study there was a net reduction of 8 per cent in REE measured 3 days after surgery, a finding similar to the ±10 per cent change in REE reported by Kinney[21]. To identify the influence of exercise upon cardiorespiratory function it is necessary to allow for alterations in REE which occur as a consequence of the metabolic response to surgery and therefore to subtract REE from the energy expenditure during exercise (AEE). Such calculations (*Figure 3*) revealed that the repetition of a preoperative workload on the third postoperative day was associated with a net increase in energy expenditure of 19 per cent (7·3(0·8) kJ min^{-1} to 8·6(0·7) kJ min^{-1}; $P<0{\cdot}03$). Similar results have been reported by Carswell and Walker[22] who found an 18 per cent fall in oxygen consumption in relation to heart rate (expressed as an extrapolation of V_{O_2} to a heart rate of 180 beats min^{-1}) in patients studied before and 7 days after moderate abdominal surgery. The increased effort required to perform simple tasks may limit the ability of the patient to mobilize in the postoperative period and contribute to the feeling of fatigue.

The respiratory quotient ($RQ = V_{CO_2}/V_{O_2}$) fell from a preoperative value of 0·72 at rest to 0·70 when performing low intensity exercise with corresponding postoperative values of 0·65 and 0·66 The characteristic rise and fall in RQ seen during periods of intense exercise and recovery would not be expected in the present study where the intensity of exercise was low and anaerobic thresholds not exceeded. The lower postoperative RQs are probably due to the complex situation after surgery where respiratory gas exchange is associated with an increased physiological dead space, reduced alveolar ventilation and carbon dioxide retention[23]. The postoperative patients had received little or no oral intake for the previous 4 days and the measured RQ was only slightly below that expected from the metabolism of endogenous fat[24].

Before operation the performance of low level exercise was associated with a doubling of the V_e measured at rest. The increase in V_e was achieved by approximately equal increases in respiratory rate (42 per cent) and tidal volume (43 per cent). Although abdominal wound pain has been shown to result in a relative rise in respiratory rate and reduction in tidal volume[25], repetition of the test on the third postoperative day was associated with similar changes in breathing patterns to those seen preoperatively. Indeed, after operation tidal volume during exercise was 57 per cent above the resting value These results suggest that postoperative pain was adequately controlled and unlikely to be a significant factor in the genesis of the changes in cardiorespiratory function Although the percentage rise in respiratory rate was not influenced by surgery, that on the third postoperative day was significantly higher than before operation ($P<0{\cdot}01$) (*Table 2*). Such changes, together with a reduction in alveolar ventilation[23] would lead to an increase in respiratory work and may be of importance in the genesis of respiratory muscle fatigue.

This study has demonstrated an increase in the cardiorespiratory effort required to undertake low intensity exercise in the early postoperative period. The cardiorespiratory changes were associated with an increased subjective feeling of fatigue and reduced muscular efficiency although fatigue as measured in the adductor pollicis muscle was unchanged. It is suggested that the increased cardiorespiratory effort required to perform simple tasks may contribute to a prolonged period of recumbency and also to the feelings of fatigue which are so common after surgery.

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Endoscopic embolization of external biliary fistulae

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Biliary cutaneous fistulae originating in the liver may occur as a complication following injury or surgery or, less commonly, as a consequence of liver abscess or hydatid disease. In the absence of distal biliary obstruction, most fistulae will close spontaneously[1]. In the few with persistent external bile drainage, endoscopic techniques using sphincterotomy[2], nasobiliary catheter drainage[3] or temporary stenting with an endoprosthesis[4] have been reported to accelerate healing.

We report a new technique using endoscopic embolization of a peripheral intrahepatic bile duct to occlude persistent external biliary fistulae in two patients in whom the fistulae had not closed after prolonged conservative treatment and where other endoscopic manoeuvres had failed. This new technique may provide a simple definitive non-operative alternative to surgical intervention which is usually complex.

Patients and methods

Case 1

A 76-year-old woman presented with a 3-week history of epigastric pain and jaundice. Abdominal ultrasound showed a 10 cm calcified hydatid cyst in the left lobe of the liver with the characteristic internal echogenic pattern and small filling defects in the gallbladder. At laparotomy no fistula or biliary filling defects were demonstrated on an operative cholangiogram and hydatid material was noted in the excised gallbladder. The hydatid contents of the cyst were sterilized with half-strength Eusol and evacuated. A biliary communication into the cyst was identified and sutured from within the cyst. Omentum and two corrugated drains were placed in the residual cavity.

The postoperative course was complicated by a biliary cutaneous fistula which drained 900 ml bile/day. An endoscopic retrograde cholangiogram (ERC) demonstrated the fistula between a branch of the left hepatic duct and the residual cavity (*Figure 1a*). The bile leak continued despite performing an adequate endoscopic sphincterotomy and subsequent selective drainage of the left hepatic duct via a nasobiliary catheter. Four weeks after operation the peripheral duct communicating with the cavity was embolized using an Ivalon® (Unipoint Laboratories, High Point, North Carolina, USA) pledget (*Figure 1b*). External biliary drainage ceased within 48 h. The patient remains well 12 months later with no jaundice or fever and normal liver function tests.

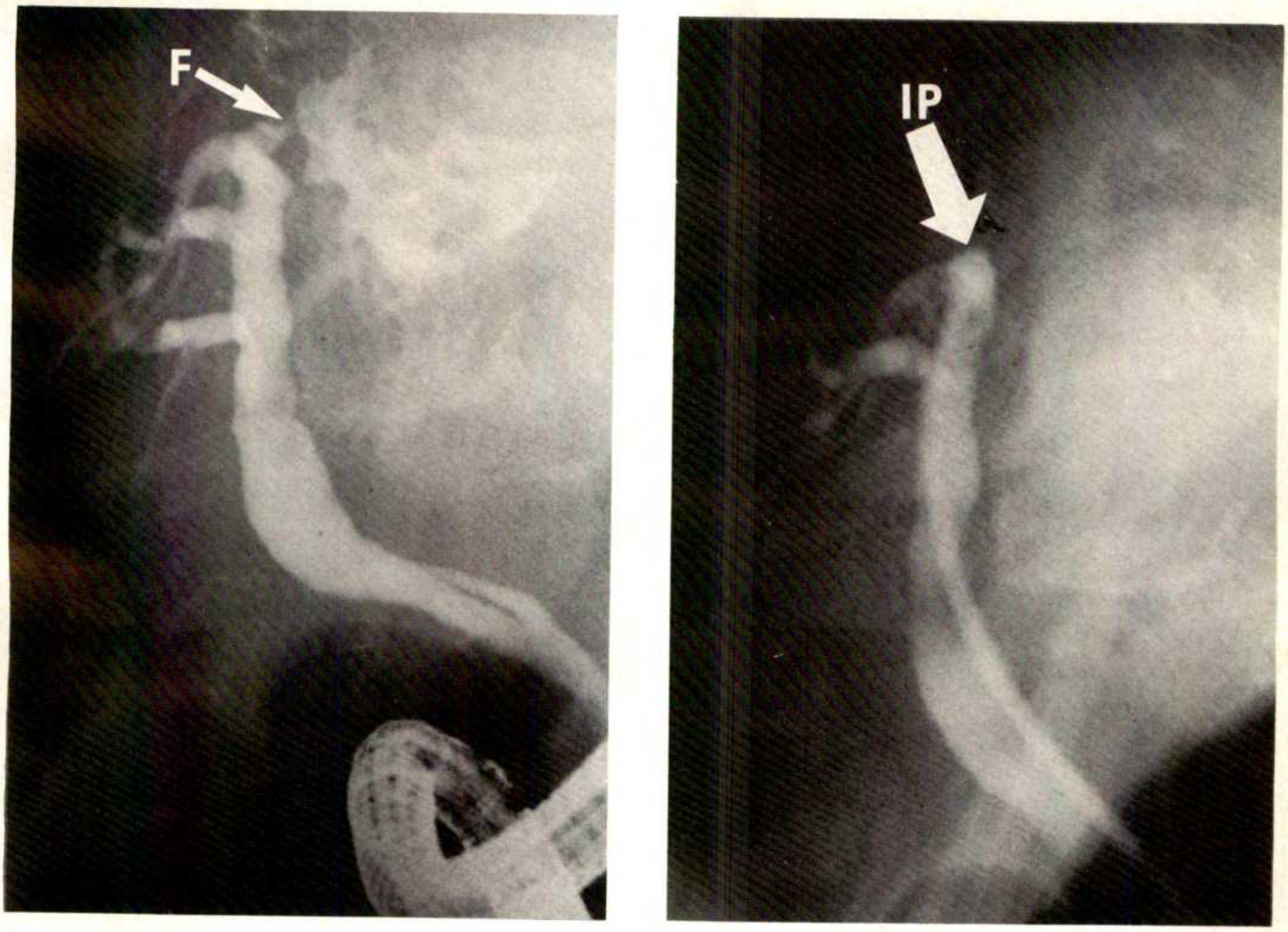

Figure 1 **a** *Endoscopic retrograde cholangiogram showing fistula (F);* **b** *postembolization cholangiogram with occlusion of duct by Ivalon® pledget (IP)*

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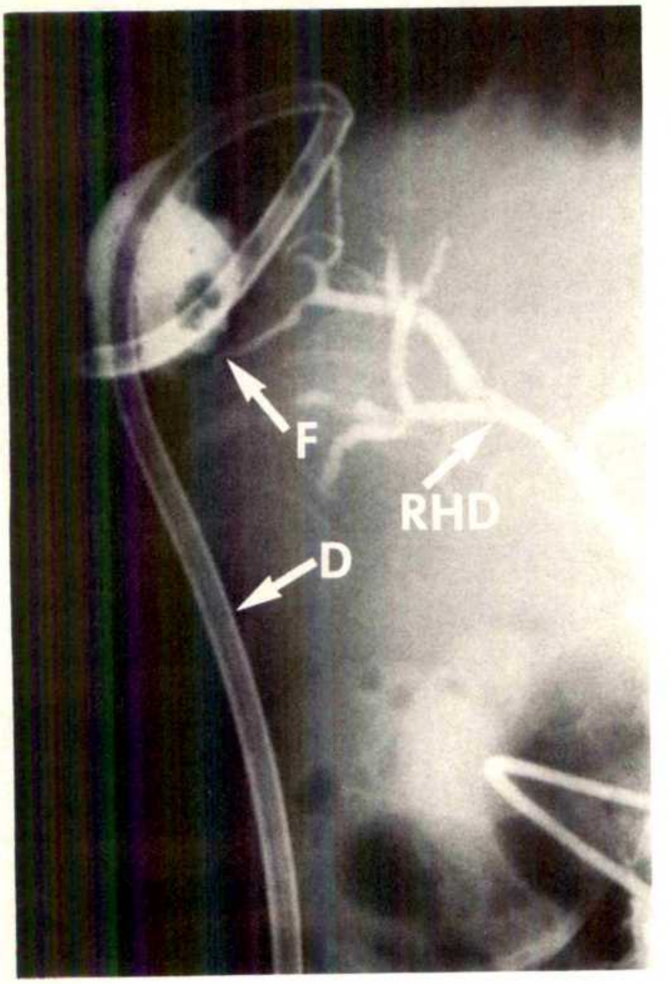

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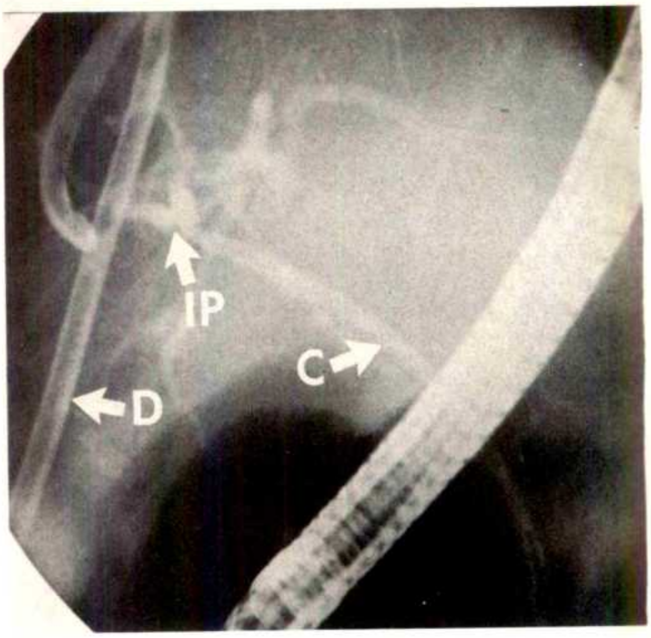

b

Figure 2 **a** *Cholangiogram demonstrating fistula (F); D, percutaneous drain; RHD, right hepatic duct;* **b** *Ivalon® pledget (IP) positioned proximal to fistula; D, percutaneous drain; C, endoscopically placed delivery catheter*

Case 2

A 49-year-old man presented with a 4-week history of right upper quadrant pain and fever due to a 15 × 14 cm right lobe amoebic liver abscess. Aspiration delivered bile-stained pus and a percutaneous 12 Fr Van Sonnenberg sump drain (Meditech Inc., Watertown, Massachusetts, USA) was inserted into the residual abscess cavity. An ERC showed several peripheral bile ducts draining into the cavity. An endoscopic papillotomy and a nasobiliary tube, selectively placed in the largest bile duct distal to the fistula, reduced external drainage from 300 to 225 ml/day. Three weeks later an ERC confirmed continuing leakage (*Figure 2a*) and the involved duct was occluded with an Ivalon pledget delivered close to the fistula (*Figure 2b*). The postembolization distal cholangiogram via the drainage tract showed complete occlusion of the duct and external drainage ceased after 6 days. Ultrasound scanning demonstrated complete resolution of the liver abscess at 16 weeks and the patient remains well 6 months after duct embolization.

Method

An Olympus JF 1T10® (Olympus Corp., Lake Success, New York, USA) side-viewing duodenoscope and high resolution fluoroscopic monitoring was used. The patient received light sedation with intravenous midazolam and pethidine. A preparatory sphincterotomy was performed and the fistula identified by retrograde cholangiography using a distally inflated balloon catheter to enhance proximal duct and fistula opacification. The JF 1T10 duodenoscope was replaced by a larger 4·2 mm channel TJF 10® operating duodenoscope to facilitate embolization. An endoscopically placed guide-wire and coaxial catheter (Cook Inc., Bloomington, Illinois, USA) combination were selectively steered as far peripherally as possible to allow positioning of a larger 10 Fr polyethylene catheter over the coaxial catheter near to the fistula. The coaxial catheter and guide-wire were removed and a 2 × 2 × 20 mm Ivalon® (polyvinyl alcohol) pledget was inserted and pushed through the larger 10 Fr catheter by the guide-wire and coaxial catheter and delivered to block the duct (*Figure 3*). Complete occlusion of the duct was confirmed by a selective intrahepatic cholangiogram. Periprocedural intravenous antibiotics were given for 48 h.

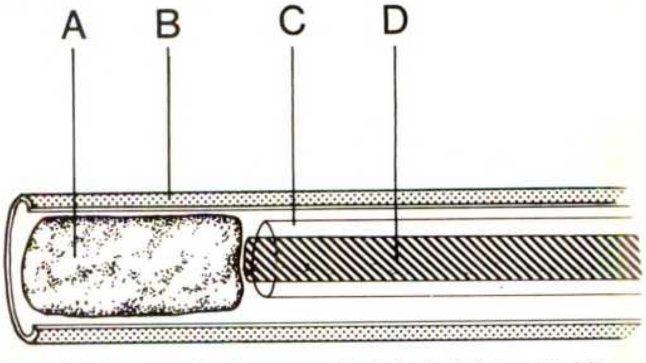

Figure 3 *Diagram of catheter assembly for Ivalon® pledget (A) delivery; B, 10 Fr catheter; C, 8 Fr coaxial catheter; D, guide-wire*

Discussion

The technique of endoscopic embolization evolved from our previous experience with percutaneous transhepatic stenting for malignant biliary obstruction where percutaneous embolization of the catheter tract[5] reduced the risk of post-stenting bile leak[6]. Despite embolization of relatively large peripheral ducts in our two patients, no further alteration in measured liver function occurred. No cholangitis or liver abscess developed during careful follow-up and serial ultrasound examinations. While the long-term effects of bile on Ivalon are unknown, no complications after percutaneous embolization of external biliary fistulae with Ivalon occurred in a previous study[5] and no delayed infection due to persistence of Ivalon has occurred in either of the patients. Accurate placement of the catheter as close as possible to the fistula before embolization was facilitated by using high resolution imaging equipment. Selective endoscopic biliary embolization may offer a definitive alternative to major surgical intervention in complex biliary fistulae arising from the liver when other endoscopic alternatives have failed.

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Testicular torsion following orchidopexy for undescended testis

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Torsion following orchidopexy for undescended testis has only been described on five occasions[1]. We report two further cases and suggest that dartos pouch fixation alone may be inadequate to prevent torsion in this high risk group.

Case 1

A 20-year-old man presented with a 6 h history of right testicular pain of sudden onset, easing gradually before admission He had undergone right orchidopexy with dartos pouch fixation for an undescended testis at the age of fourteen. He described several episodes of similar pain since then, though none as severe At his previous surgery, performed by a consultant surgeon, the cord had been mobilized to the deep ring, the vessels mobilized for a short distance extraperitoneally and the testis secured in a dartos pouch with a restraining suture to the dartos fascia.

Examination revealed a tender right testis and small hydrocele At operation a long testicular mesentery permitted rotation through 540° The cord was oedematous indicating recent torsion but the blood supply to the testis was not compromised. The testis was fixed with a 2/0 polyglycolic acid suture on both sides and further secured by taking up the tunica albuginea with the suture while closing the tunica vaginalis. The contralateral side was also explored but this had an almost normal investment of tunica permitting little movement. It was fixed as described above.

Case 2

An 18-year-old man was admitted with a 3 h history of severe right scrotal pain of sudden onset He described several similar episodes of pain over the previous 6 months He had undergone left orchidopexy with dartos pouch fixation for undescended testis two years previously and at his previous operation, performed by a senior registrar, the testis and cord had been mobilized to the deep ring, a small hernia sac transfixed and excised, the testis drawn down to a dartos pouch and the dartos fascia secured around the cord with a chromic catgut suture

On examination the left hemiscrotum was swollen and the left testis tender and elevated. At operation the testis was found to have undergone torsion through 360° in an anticlockwise direction. This was untwisted with an immediate improvement in colour and the testis was fixed with 2/0 polyglycolic acid sutures. The right testis was also found to have an abnormally narrow tunical attachment and was similarly fixed.

Discussion

Torsion of the testis was first reported in 1840 by Dalasiavue affecting an undescended testis and maldescent has since been recognized as increasing the risk of torsion tenfold[2]. The anatomical arrangement that predisposes to intravaginal torsion includes high investment of the tunica vaginalis resulting in a freely mobile testis suspended by a long mesorchium, an anomaly more common in maldescended testes[3].

While the surgical management of torsion of the descended testis mandates opening the tunica and fixing the testis, standard textbook descriptions of orchidopexy for undescended testes (such as dartos pouch fixation and the Ombrédanne procedure) do not insist that the tunica is opened or that the testis is fixed within it[4,5], thus the predisposition to torsion is not addressed. It is possible that the risk of torsion is reduced by division of the cremaster muscle, which has been implicated in its pathogenesis, but this cannot be relied upon. It would seem prudent to open the tunica and fix the testis or at least transfix the testicular capsule routinely during orchidopexy if torsion is to be avoided.

The salvage rate following testicular torsion has improved in recent years because of increased awareness and prompt action. A history of previous orchidopexy for undescended testes should not reduce the index of suspicion. Indeed, recurrent testicular pain following orchidopexy should suggest the diagnosis, especially where dartos pouch fixation has been employed.

Acknowledgements

We wish to thank Mr W. P. Hederman for allowing us to report on his patient, case 2.

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Surgical workshop

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Continuous intra-arterial infusion therapy: an alternative approach to the femoral artery

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The femoral artery has been the commonest access site for intra-arterial intubation therapy to the hepatic artery[1–5]. Either an operative approach to the deep femoral artery or a percutaneous puncture of the superficial femoral artery has been employed. However, the technique has sometimes been accompanied by complications such as the formation of a local aneurysm or haematoma, or intra-arterial thrombosis[6–9]. This report details a potentially safer technique for operative intubation using the superficial circumflex iliac artery.

Patients

Eight patients were involved in this study (*Table 1*). Five had hepatocellular carcinoma and three had a metastatic liver tumour. Their average age was 65 years. All had undergone previous angiography and/or intra-arterial infusion therapy The observation period after surgery was between 1 and 9 months

Surgical technique

A transverse skin incision at a level just below the inguinal ligament was made under epidural anaesthesia. A 2 cm length of the right femoral artery was exposed The superficial circumflex iliac artery, usually branching from the lateral or posterior wall of the femoral artery at the level of the inguinal ligament, was palpated and exposed. The artery was divided 2 cm from its origin at the femoral artery, control being maintained with a bulldog clip and rubber sling (*Figure 1*). A 5 Fr spiral catheter with a 0 09 cm guidewire was then inserted through the divided superficial circumflex iliac artery, the cut end of which was supported by two polyester threads The tip of the catheter was manipulated into the hepatic artery and then replaced with a heparin-coated long-life catheter (Anthron P-U catheter, Toray, Tokyo, Japan) Finally the superficial circumflex iliac artery was tied to the catheter, the end of which was connected to a resealable port (Port-a-cath® (A), system 320, Pharmacia, Saint Pole, USA) which was implanted in the subcutaneous space in the right hypogastric region

Discussion

The site to be used for arterial intubation must be one that is accessible and not prone to cause ischaemic complication or catheter dislocation. The superficial circumflex iliac artery, which always bifurcates about 1 cm below the inguinal ligament, can be occluded without fear of distal ischaemia Moreover, it is covered by the inguinal band such that catheter dislocation is avoided. These features make the technique described in this paper attractive compared with the standard percutaneous transfemoral approach, which may be accompanied by complications such as thrombosis, pseudoaneurysm and haematoma[6–9]. It also has advantages over the other common approach which uses the deep femoral artery. The latter is the main artery of the thigh and it also provides the principal blood supply, via collateral pathways, to the leg below the knee when the superficial femoral artery is occluded. In asymptomatic patients with occlusion of the superficial femoral artery, loss of the deep femoral artery will cause distal ischaemia.

For superselective catheterization of the hepatic artery, one has to be able to twist the catheter. In the present procedure, the superficial circumflex iliac artery was exposed for a length of 2 cm which allowed the catheter to be handled with ease.

In this study, no major complication or dislocation occurred during the observation period (from 1 to 9 months) during which the patients pursued their normal lives. The single minor complication was lymph oedema around the area of the implanted port in one patient, which may have been caused by poor dissection of the femoral artery

Table 1 *Details of eight patients catheterized via the superficial circumflex iliac artery*

Age (years)	Sex	Disease	Duration of follow-up (months)	Catheter status
65	F	Metastasis	6	Removed
65	M	Metastasis	9	Continued
70	M	HCC	5	Continued
68	M	HCC	1	Removed
58	M	HCC	4	Continued
70	F	Metastasis	4	Continued
80	M	HCC	3	Continued
42	M	HCC	1	Continued

HCC, hepatocellular carcinoma

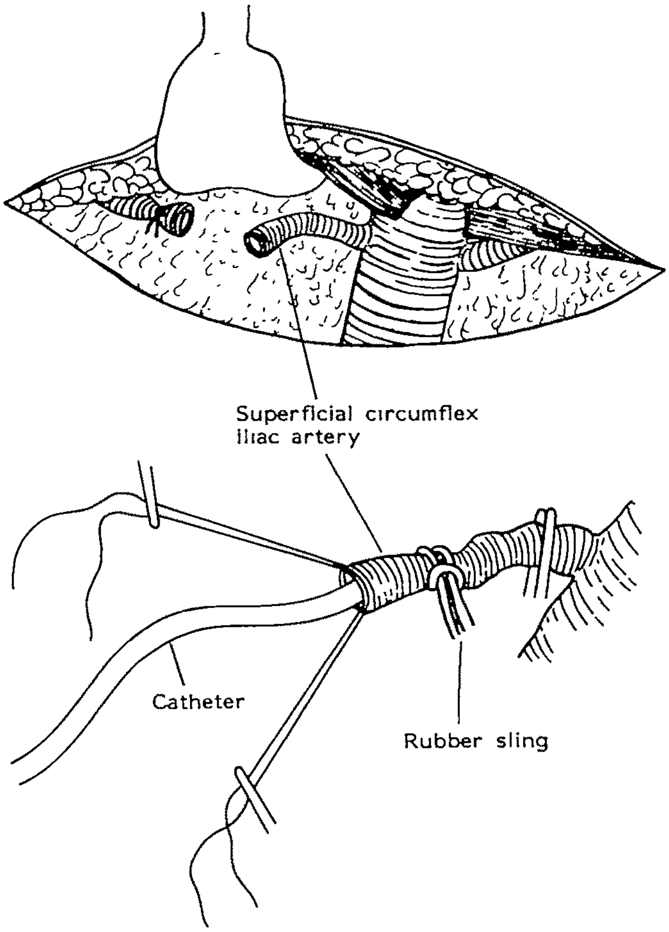

Figure 1 *Schematic drawing of the superficial circumflex iliac artery catheterization*

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Short note

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Hepatitis B immunization in vascular surgeons

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Health workers constitute a high risk group for contracting hepatitis B. The latest available rates for health service personnel quote an annual rate for surgeons as a whole of 25 per 100 000[1]. However it is known that notification rates unreliably predict the true incidence of both clinical and subclinical disease[2] which may be between two and ten times as great. Furthermore the ratio of clinical to subclinical disease may be as high as 20:1 (Reference 2). Therefore, members of the Vascular Surgical Society of Great Britain and Ireland were invited to answer a confidential questionnaire concerning hepatitis B immunization.

Results

Two hundred and six (78 per cent) surgeons replied of whom 38·8 per cent were aged 45 years or less and 81·1 per cent were aged 55 years or less (*Table 1*). Ninety-three (45·1 per cent) admitted to at least one needle stick injury, and 14 (6·8 per cent) admitted to more than ten Twenty-five (12·1 per cent) surgeons had received γ-globulin for unprotected contamination from a hepatitis B positive patient. The surgeons' own estimate of risk of contracting hepatitis B varied widely. Twenty-three per cent expected less than five surgeons per year to be at risk, and 19 per cent thought the risk was more than 15 surgeons per year. There was no correlation with age, renal commitment or previous need for γ-globulin. The younger surgeon was more likely to be immunized than the older surgeon ($P<0{\cdot}02$, *Table 1*); however, there was no difference in the subsequent checking of immunity.

Most surgeons did perform routine checking of high risk groups (60·2 per cent), with no difference in the age groups. The most effective way of immunization was via organized clinics,

Table 2 *Efficacy of the various vaccination offers*

How offered vaccination	No. of surgeons	Percentage accepted
1. None	40	(21 'self-immunized')
2. Personal invitation	40	64
3. Organized clinic	22	86*
4. General memorandum	91	60
5. General practitioner	11	91*
6 Already immune	2	—

* $P<0{\cdot}05$ χ^2 test; 3 *versus* 4, 3 *versus* 1, 5 *versus* 1

Table 1 *Frequency data from hepatitis B questionnaire*

	Age group (years)				
	35–45	46–55	56–65	65+	Total
No. of surgeons	80 (38 8)	87 (42·2)	34 (16 5)	5 (2·4)	206 (100)
Percentage immunized	75*	62	50*	0	63·6
Needle stick injuries					
0	47	47	17	2	113 (54·9)
1–5	26	32	14	1	73 (35 4)
6–10	3	1	1	1	6 (2·9)
10+	4	7	2	1	14 (6·8)
Previous γ-globulin	7	13	4	1	25 (12·1)
Renal commitment	15	10	4	0	29 (14·1)

Values in parentheses are percentages, * $P<0{\cdot}02$ χ^2 test (i.e. 35–45 > 56–65).

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usually within the theatre complex ($P < 0.05$), by the occupational health department, or by the general practitioner ($P < 0.05$; *Table 2*). Of 29 surgeons with a renal commitment, eight were not immunized and a further eight of those immunized had not had their immunity checked.

Discussion

Although 113 (54·9 per cent) respondents claimed they had no history of needle stick injury, there is good evidence to suggest a much higher glove perforation rate than has hitherto been appreciated[3]. Despite being in a high risk group nearly 20 per cent of vascular surgeons had never been offered hepatitis B vaccination, and 45 per cent of those immunized had not had their immunity checked. Currently the majority of vascular patients are over 60 years of age, hence, in the future, the proportion of hepatitis B and human immunodeficiency virus carriers will undoubtedly increase the risk still further.

The notification rate of acute hepatitis B has more than doubled from the rate in 1975–79[1], and the carrier state is thought to persist in up to 10 per cent of cases[4] with consequent risk of transmission to patients[5]. Extrapolating these results suggests a potential annual total of up to 28 surgeons with acute clinical infections.

These results indicate that much more can be done to improve the uptake of hepatitis B immunization and the monitoring of its effectiveness. Organized theatre clinics with personal invitation or involvement of the general practitioner would appear to be the most effective ways of both bringing the message and obtaining the desired results.

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Intestinal permeability is increased in burn patients shortly after injury

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There is increasing direct experimental and indirect clinical evidence to indicate that under certain conditions intestinal barrier function may be lost in trauma victims. No direct measurements, however, have been performed in patients to determine whether intestinal permeability is increased shortly after a major thermal injury in the absence of infection Fifteen hemodynamically stable burn patients with burns on more than 20% of their body surface (39% ± 12%) had their intestinal permeability measured within 24 hours of injury with use of the two nonmetabolizable sugars lactulose and mannitol as permeability markers. Lactulose absorption was fourfold higher in the patients (223 ± 54 μmol) than in the controls (58 ± 11 μmole; $p < 0.02$), whereas the lactulose/mannitol ratio was threefold higher (5.2 vs 1.7; $p < 0.05$). Thus intestinal permeability was increased in patients with moderate to major burn injuries shortly after injury. (SURGERY 1990;107:411-6.)

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RECENTLY, ATTENTION HAS been focused on the role of the gastrointestinal tract as a promoter or potentiator of organ dysfunction and sepsis in the high-risk surgical patient. The potential etiologic role of intestinal barrier failure in the development of systemic infections and the septic state is based on both clinical and experimental evidence. First, results of animal studies and clinical series indicate that the intestine can serve as a portal of entry for bacteria and intraluminal toxins, such as endotoxin.[1-3] In fact, the gut has been termed the "motor of multiple organ failure."[4] Second, in a guinea pig burn model early enteral feeding has been documented to blunt burn-induced hypermetabolism and catabolism by maintaining gut mass and preventing the excessive secretion of catabolic hormones.[5] Most recently, investigators from Wilmore's laboratory have documented that a single dose of endotoxin will increase intestinal permeability in healthy human volunteers.[6] In a subsequent study, these investigators found that intestinal permeability is increased in infected burn patients.[7] Taken together, these studies indicate that, in human beings, altered intestinal permeability, and perhaps loss of barrier function, occurs during infectious episodes or periods of endotoxemia.[6,7] It is not possible, however, to determine from these human studies whether intestinal permeability is altered by trauma in the absence of infection. Yet, on the basis of animal studies, it appears that intestinal barrier function is transiently impaired shortly after thermal injury in the absence of infection.[8,9] To answer the question of whether a major thermal injury is associated with increased intestinal permeability, we measured intestinal permeability shortly after injury in 15 nonseptic, hemodynamically stable patients with burns on more than 20% of their total body surface area. The results of this study indicate that intestinal permeability in human beings is increased after a major thermal injury in the absence of infection.

MATERIAL AND METHODS

Patient population. Fifteen burn patients admitted within 6 hours of their injury to the LSU-Shreveport Burn Center between August 1988 and March 1989 were enrolled in this study. Patients who sustained inhalation injuries, who were hemodynamically unstable, or who had received inadequate volume resuscitation before arrival at the center were excluded. Other exclusionary criteria included a history of gastrointestinal disease, preexistent renal disease, or the presence of a current or a recent infection. All patients had burns on more than 20% of their total body surface area, and no patient experienced cardiovascular instability during

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Table I. Demographics of study populations

Group	*n*	*Sex M/F*	*Age (yr)*	*TBSA (%)*	*% 3rd*
Control	8	6/2	38 ± 6	—	—
Patient*	15	13/2	44 ± 22	39 ± 12	12 ± 13

All data expressed as mean ± SD
*Eight white and seven black

the study period (Table I). The study was reviewed and approved by the LSU-Shreveport Institutional Human Subjects Review Committee. Before initiation of the study, informed consent was obtained from patient or family.

Study design. The goal of the study was to determine whether intestinal permeability was increased shortly after thermal injury. Therefore in all the patients intestinal permeability was measured between 16 and 30 hours after injury. The patients fasted from midnight to 7 AM. At 7 AM a plasma sample was collected for the measurement of endotoxin and a pretest urine sample was collected for baseline urinary sugar measurements. After the pretest samples were obtained, the patients received 10 gm of lactulose and 5 gm of mannitol dissolved in 50 ml of water through their nasogastric tubes. Urine was collected on ice for the next 6 hours, during which time the patients received no medications or enteral feedings. The plasma and urine specimens were aliquoted and stored at −20° C until assayed.

Because both lactulose and mannitol are nonmetabolizable sugars, they are excreted unchanged in the urine. Thus the amount of lactulose and mannitol excreted in the urine directly reflects the amount absorbed. Lactulose, in contrast to mannitol, is not normally absorbed. Therefore an increase in urinary lactulose levels indicates increased intestinal permeability.[10] Because factors other than intestinal permeability, such as intestinal motility or renal excretion, may influence lactulose excretion, mannitol was used as a second marker to control for these variables.

The control population consisted of eight healthy volunteers (mean ± SD age, 38 ± 6 years) without any history of recent or remote gastrointestinal, cardiovascular, or renal disease. None were taking any medication.

Lactulose and mannitol assay. Urinary lactulose was measured spectrophotometrically with use of the assay developed by Behrens et al.[10] In this assay the lactulose is enzymatically cleaved to fructose and galactose. The fructose is then converted to fructose-6-phosphate by hexokinase, which is subsequently enzymatically converted to glucose-6-phosphate by the enzyme phosphoglucose isomerase. In the final reaction, glucose-6-phosphate in the presence of $NADP^+$ is converted to gluconate-6-phosphate and NADPH by glucose-6-phosphate dehydrogenase, and the generated NADPH is measured spectrophotometrically at 340 nm. Urinary mannitol was measured by the assay of Corcoran and Page.[11] In this assay mannitol is oxidized by periodic acid to formic acid and formaldehyde. The level of formaldehyde produced is determined spectrophotometrically (570 nm) with use of chromotropic acid reagent 1,8-dihydroxynapthalene-3,6-disulfonic acid. All reactions were performed in duplicate and the results averaged. Baseline values for mannitol were determined on the pretest samples and subtracted from the test samples.

Endotoxin assay. Plasma endotoxin levels were measured with the chromogenic limulus amebocyte lysate test kit (QCL-1000; Whittaker Bioproducts, Walkersville, Md.). Because burn patients and other stressed patients may have higher levels of inhibitory factors in their blood than normal controls,[12] each plasma sample was tested at multiple dilutions (10, 20, and 30). In addition, each test sample was spiked with a known amount of endotoxin (0.05 to 0.20 EU) to ensure that the presence of endotoxin was accurately measurable at the dilutions assayed. Each assay was run in duplicate and the results averaged.

Statistical analysis. The unpaired *t* test and linear regression analysis were used as indicated. Differences were considered significant when $p < 0.05$. All values are expressed as mean ± SEM, unless otherwise specified.

RESULTS

Intestinal absorption of lactulose, but not mannitol, was increased after thermal injury (Fig. 1). The amount (mean ± SEM) of lactulose excreted in the urine during the 6-hour timed urine collection was almost fourfold greater in the patients (223 ± 54 μmol) than in the controls (58 ± 11 μmol; $p < 0.02$). In contrast, there was no difference in the amount of mannitol excreted between the patient (4.04 ± 0.78 mmol) and the control groups (3.45 ± 0.48 mmol). The fact that the lactulose-mannitol ratio was threefold higher in the patients than in the controls (Fig. 2) further indicated that the increased amount of lactulose excreted in the urine was due to increased absorption and not to differences in intestinal motility or renal excretion. Because intestinal lactulose absorption is through a paracellular route,

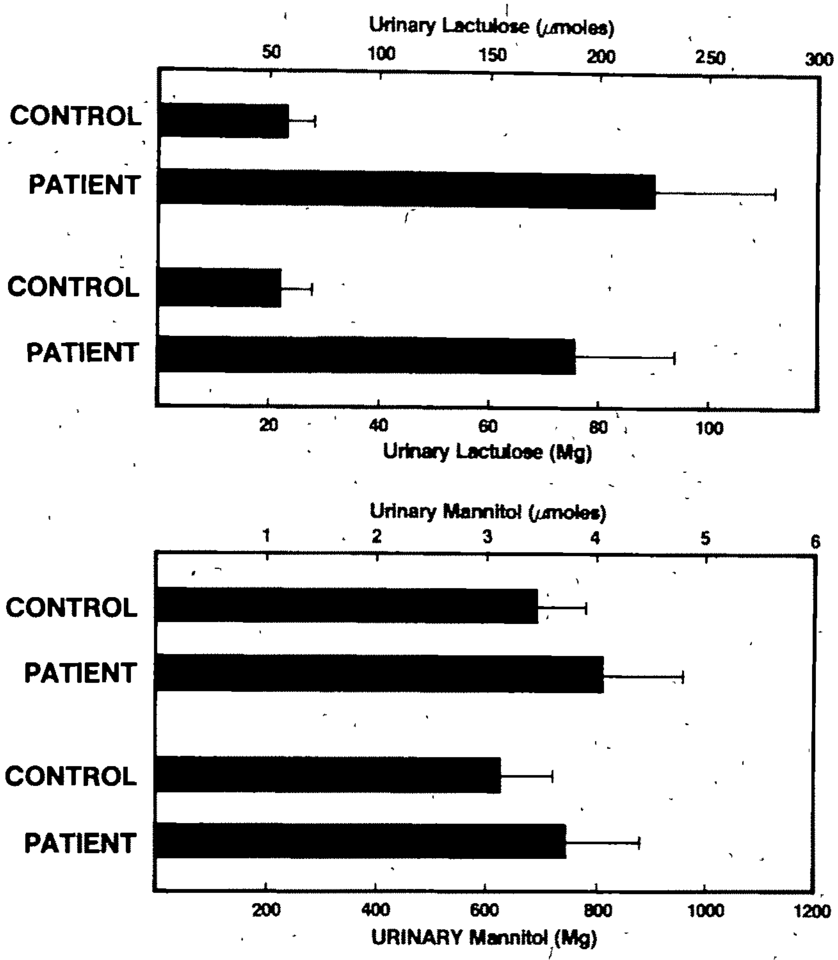

Fig. 1. Urinary lactulose excretion during 6-hour timed urine collection was increased in burn patients compared with controls ($p < 0.02$). Mannitol excretion was similar in both groups. All values expressed as mean ± SEM.

whereas mannitol absorption is primarily transcellular, these results suggest that paracellular, but not transcellular, permeability is increased after thermal injury.

There was no correlation between the magnitude of the injury (burn size) and increased intestinal permeability, whether measured as the lactulose/mannitol ratio ($r = 0.12$) or as the amount of urinary lactulose excreted during the 6-hour period (μmol lactulose, $r = 0.31$; or milligrams lactulose, $r = 0.30$).

We also measured plasma endotoxin levels in these patients because systemic endotoxemia, which could have originated from the intestinal tract, has been documented after thermal injury.[13] The level of plasma endotoxin (mean ± SD) of the patients (0.39 ± 0.14 EU) was not different from that found in the control volunteers (0.31 ± 0.12 EU). Therefore plasma endotoxin levels measured within 24 hours of injury were not elevated in this group of burn patients. Furthermore, there was no correlation between plasma endotoxin levels and intestinal permeability, whether measured as the lactulose/mannitol ratio or as urinary lactulose excretion (data not shown).

DISCUSSION

Since human intestinal permeability was first evaluated by Fordtran et al.,[14] using an indirect method of measuring the reflection coefficient of the intestine, a number of intestinal permeability probes have been evaluated.[15] On the basis of these studies, it is accepted that the ideal permeability probe should not be recognized by the immune system, should be measurable with sensitivity, accuracy, and ease, and should be nontoxic and metabolically inert. Furthermore, when urinary excretion is used to evaluate intestinal absorption, renal clearance of the marker should be quantitative. Because certain of the inert, nonmetabolizable sugars fulfill these

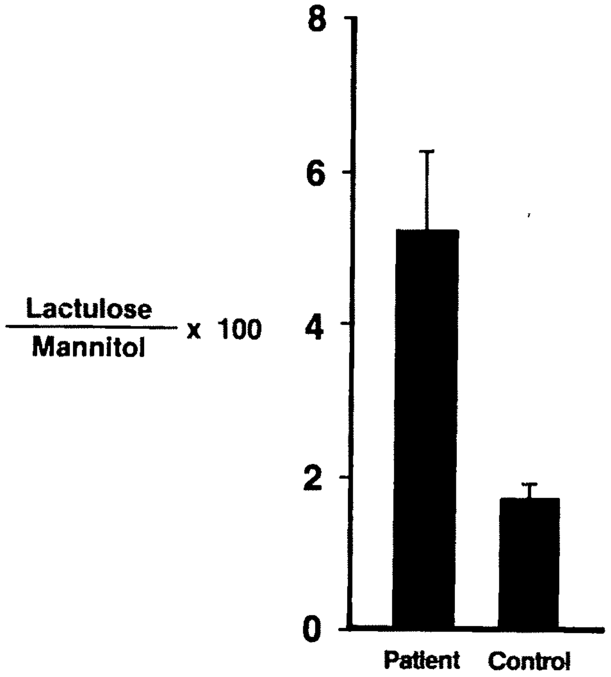

Fig. 2. The lactulose/mannitol ratio was higher in burn patients than in controls ($p < 0.05$), indicating that increased amount of urinary lactulose was not due to alterations in intestinal motility or renal excretion. All values expressed as mean ± SEM

requirements, they have been evaluated as probes of intestinal permeability in children and adults with gastrointestinal diseases, such as celiac disease, Crohn's disease, or diarrheal states associated with malabsorption.[16-18] In these studies, permeability to disaccharides, such as lactulose and melibiose, is significantly increased, and absorption of monosaccharides, such as mannitol, xylose, or L-rhamnose, is impaired.

Because many variables may influence the results of tests in which a single absorption marker is used, differential absorption techniques that involve the simultaneous use of two markers have been developed and evaluated. A major advantage of this dual-marker technique is that the confounding effects of irrelevant variables that may influence results based on a single marker can be overcome by expressing absorption as a ratio of the two markers.[19] For example, factors—such as intestinal motility, surface area of absorption, renal clearance, and accuracy of urine collection—that may alter the results obtained with a single marker of permeability will not alter the absorption ratio of two markers because both markers will be equally affected.

Two inert sugars most commonly used to evaluate altered intestinal permeability in patients with gastrointestinal disease are lactulose and manntiol.[16, 17] Both sugars are hydrophilic and lipophobic, have negligible affinity for the monosaccharide transport system and thus are absorbed passively in a nonmediated fashion.[16] Furthermore, urinary excretion has been documented to mirror gastrointestinal absorption of both these sugars. Mannitol and lactulose differ in their molecular size and route of absorption. Mannitol, a monosaccharide, has a radius of 0.4 nm and is absorbed transcellularly through aqueous pores in the cell membrane. In contrast, the route of absorption of lactulose, a disaccharide, radius 0.52 nm, is paracellular, and absorption occurs via extrusion zones at villous tips and at tight junctions.

With mannitol and lactulose used as permeability probes, the major finding of this study is that intestinal permeability is increased shortly (within 24 hours) after thermal injury in the absence of infection. These results extend the recent results of Ziegler et al.[7] who found that intestinal permeability was increased in burn patients during infectious episodes. Although these authors did not find altered intestinal permeability in the absence of infection, their patients were not studied during the immediate postburn period. Instead, most of the patients were studied during the second and third postburn weeks, at a time when burn-induced alterations of intestinal permeability, if present, might have returned to normal. The concept that burn-induced alterations in intestinal permeability, in the absence of infection, may be short-lived is supported by our experimental studies on bacterial translocation from the gastrointestinal tract.[8, 9] In murine studies increased gut permeability, measured as bacterial translocation to systemic organs and tissues, was increased during the first 72 hours postburn. By 7 days postburn, however, gut permeability had returned to normal, and bacterial translocation was no longer detected. Thus our result documenting increased intestinal permeability immediately after thermal injury is not in conflict with the findings of Ziegler et al.,[7] because the period when most permeability changes have been experimentally documented is during the early, and not the later, postburn period. Furthermore, the percent of orally administered lactulose absorbed in our healthy controls (0.22%) was similar to that reported by the Ziegler group (0.20%) and by other investigators.[10]

On the basis of histopathologic studies of patients with small-bowel disease,[15-19] our findings that lactulose absorption is increased while mannitol absorption is normal would suggest that burn-induced intestinal permeability is related to loss of tight junction integrity or to areas of cell loss or damage at the villous tips. These predicted histopathologic findings are similar to what we observed in our murine model of thermal injury.[20] Loss of barrier function and mucosal injury, however, manifested as increased paracellular permeability and edema of villous tips of the small bowel, has also been documented after limited periods of hemorrhagic shock and during experimental endotoxemia.[21-23] Thus it is possible that other acquired conditions may also result in altered intestinal permeability. This concept is supported by the recent finding that a single dose of endotoxin increases intestinal permeability in healthy volunteers.[6]

Plasma endotoxin levels were measured in our patients for several reasons. First, endotoxemia has been documented after thermal injury.[13] Second, the presence of elevated circulating levels of endotoxin within 24 hours of thermal injury would be a further indication of increased intestinal permeability because bacterial colonization of the burn wound has not yet occurred. Third, endotoxemia increases intestinal permeability in both animals and human beings [6, 23, 24] Although others have found an early elevation of plasma endotoxin levels after thermal injury,[13, 25] the plasma levels of endotoxin in our patients (0.39 EU) were not significantly different from levels in the control population (0.32 EU). Winchurch et al.,[13] found that the temporal pattern of endotoxemia after thermal injury was bell-shaped, with peak endotoxin levels occurring on days 3 and 4 postburn. In an unpublished study we documented a similar phenomenon; that is, plasma endotoxin levels significantly increase on day 1 and 3 postburn, although in that study, as in this study, plasma endotoxin levels measured within 24 hours of injury are not different from control values. In a recent study of 19 burn patients, Dobke et al.[25] found serum endotoxin levels to be increased within 24 hours of injury. The endotoxin values of their patients 24 hours postburn (0.41 ± 0.13 EU) were similar to the values we obtained (0.39 ± 0.14 EU). In contrast, the mean serum endotoxin level of their controls was less than 0.1 EU, which is threefold lower than our mean control value. Nonetheless, although it appears clear that endotoxemia does occur after a major thermal injury, more work will be necessary to determine whether there is a causal association between altered intestinal permeability and endotoxemia.

It is not possible to determine from this study the exact mechanism(s) by which a major thermal injury alters intestinal permeability On the basis of our experimental work in a murine model of thermal injury, however, it appears that the mucosal injury occurring during the resuscitative phase of thermal injury is due to an ischemia-reperfusion injury.[20] This hypothesis is based on experimental information documenting that inactivation or inhibition of xanthine oxidase activity prevents mucosal injury and reduces the extent of bacterial translocation.[20] Further support for this concept comes from the recent work of Navaratnam et al.,[26] who reported an association between decreased mesenteric blood flow and increased bacterial translocation in a sheep burn model. Additionally, pharmacologic maintenance of mesenteric blood flow at baseline levels markedly decreased the incidence of bacterial translocation. Thus, at present, intestinal ischemia with a resultant oxidant-mediated reperfusion injury appears the most likely explanation for the increase in intestinal permeability occurring shortly after thermal injury. This is not to say that altered intestinal permeability can not be due to other factors. Altered intestinal permeability later in the postburn period may be related to gut malnutrition or episodes of infection, endotoxemia, or hypotension.[22, 23, 27]

The clinical significance of altered intestinal permeability in burn patients remains speculative On the basis of animal studies and clinical series, it appears that the intestine can be the portal of entry for organisms causing life-threatening or lethal infections after thermal or mechanical trauma.[3, 28-30] Furthermore, there is increasing evidence that failure of the gut barrier may play a role in the initiation or progression of the hypermetabolic response and multiple organ failure syndrome that occur after major trauma.[4, 5, 31, 32]

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Functional closure of the femoral canal

Sir

Hahn-Pedersen *et al* (*Br J Surg* 1989; **76**: 1195–7) have shown that raised intra-abdominal pressure increases the diameter of the external iliac vein deep to the inguinal ligament They have concluded that this effect is dependent on there being a competent valve in the upper region of the femoral vein and that the occlusion of the femoral canal thus produced prevents femoral herniation. I wish to take issue with both conclusions.

The presence of competent valves in the iliofemoral venous segment is largely irrelevant to changes in diameter owing to raised venous pressure *in vivo* In the cadaver, there is no forward hydraulic venous flow, and therefore the closure of a competent valve will produce dilatation of the segment proximal to the valve relative to the distal segment, analogous to performing Harvey's test[1]. In the living subject, however, the situation is quite different. There is a constant forward venous flow resulting in a hydraulic pressure of approximately 12 cmH_2O in the ileofemoral segment when supine[2]. Any impedence to outflow, as caused by raised intra-abdominal pressure, inevitably causes dilatation of the entire vein, irrespective of valve action I have demonstrated this phenomenon in the iliofemoral segment of ten greyhounds in response to the Valsalva manoeuvre, and to partial and complete iliac vein occlusion (unpublished observations).

The demonstration that venous dilatation occludes the femoral canal during periods of raised intra-abdominal pressure does not justify the conclusion that femoral herniation is prevented For this, it would be necessary to show that the pressure exerted by the femoral vein on the femoral canal exceeds the pressure exerted on the canal by any potentially herniating organ.

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Salmonella, Shigella and sugar

Sir

We read the case reports describing toxic megacolon and perforation due to *Salmonella*[1] and *Shigella*[2] infection with interest. Both describe a diarrhoeal illness of 9–14 days before admission, during which time the course of the disease might have been altered Therapeutic options may appear limited in the circumstances and certainly consideration of the use of a laxative in individuals with infective diarrhoea might be regarded as verging on the insane. However, there is a precedent for the use of lactulose in the management of both the acute and the carrier states of salmonellosis[3–7] and shigellosis[8,9] Interestingly, this effect does not appear to be limited either to man or to lactulose. both lactose and mannose have been shown to significantly reduce the faecal carriage of *Salmonella* species in infected chickens[10,11]. Lactulose may affect other infections, such as urinary tract infections[12,13], whilst appearing to have, in addition, an anti-endotoxin action[14,15].

Whilst not suggesting that lactulose might have prevented perforation in the patients described, the conservative use of lactulose could alter the progression of disease whilst investigations proceed to distinguish inflammatory bowel disease from infective diarrhoea.

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Bile leaks after simple cholecystectomy

Sir

We read with interest the article entitled, 'Bile leaks after simple cholecystectomy' by Rayter *et al*. (*Br J Surg* 1989; 76 1046–8) Authors have favoured cholecystectomy without drainage, and that is what they have tried to propagate through their study on a small number of patients undergoing elective cholecystectomy. This report has done very little to solve controversy of drainage *versus* no drainage. Nevertheless this study has come out with some interesting points Eleven (31 per cent) of their patients had positive HIDA scans with a mean right upper quadrant: whole abdomen radioactivity value of 51 per cent. Loculated fluid collections demonstrated by ultrasound were present in 20 patients There was no relationship whatsoever between HIDA and ultrasound scan findings. More importantly six of 11 patients with positive HIDA scans had no collection detected by ultrasound scan and 15 of 24 patients had collections on ultrasound whose HIDA scans were negative Therefore neither HIDA nor ultrasound scan accurately to detect the type of leak or collection that we looked for in the subhepatic space. All the 35 patients were lucky enough not to have a significant bile leak or collection of serosanguinous fluid, although one HIDA negative patient with such a collection did require aspiration

The overall complications reported in the present study are 37 per cent (13/35), with 14 per cent respiratory tract infections, 6 per cent wound infection, and 29 per cent unexplained fever. By any standard the complication rate is alarming

Authors have taken a very narrow view of drainage after cholecystectomy. Drain provides egress to both bile and blood related serosanguinous collections and does not increase the rate of complications as has been shown in our study[1]. The higher complication rate in the present study is probably due to non-drainage of leaks and collections in subhepatic space, which subsequently proved deleterious in causing a decrease in diaphragmatic movement on the right side. Thereby more respiratory tract infections, peritoneal reaction to bile leading to unexplained pyrexia and bacterial overgrowth in a suitable medium in subhepatic space led to wound infection despite antibiotic prophylaxis. Transverse incision may be an added factor for higher rate of wound infection.

Authors themselves have shown biliary leaks in 31 per cent of their patients after cholecystectomy and have argued that clinically significant leakage is uncommon. May we ask what would have happened in a patient with significant leak, however uncommon that may be? After all what are they afraid of; drainage after elective cholecystectomy, preventing various complications (which they could not achieve) or drain related problems (which are still rarer). In our prospective study[1] on 100 patients, where drainage after elective cholecystectomy was provided without prophylactic antibiotics, none of the patients developed wound infection and one patient developed subphrenic abscess and respiratory complication. More importantly in our group drainage did help in detecting significant bile leak[2] in two patients. We feel that problems due to drainage are over-emphasized. A drain can be used routinely and when removed on the first postoperative day in the absence of excessive soakage, will not lead to increased complications.

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Authors' reply

Sir

Thank you for the opportunity to reply briefly to the letter from Messrs Misra and Kapur. We are flattered that they read our contribution so closely but regret their interpretation. It is true that there was no relationship between HIDA and ultrasound scan findings; this was because the two types of scan demonstrate a different leak HIDA scans show bile leaks while ultrasound scans show serosanguinous collections. The suggestion that our 35 patients were lucky enough not to have a significant leak of bile is a misunderstanding. We believe that 31 per cent of our patients *did* have a significant leak of bile; a significant volume of bile, that is, but of no clinical significance One collection was aspirated with the patient's informed consent for scientific purposes and not for clinical reasons. Ethical considerations prevent us doing more as you, Sir, will understand.

Apart from the urinary retention, the complications were universally minor and none delayed the patient's discharge from hospital. We would not consider two wound infections in this series 'alarming'. The unexplained pyrexia was an interesting phenomenon of which the patients were completely unaware and which settled spontaneously. The literature, some of which we quoted, supports the view that the complication rate is higher after drainage; no study exists that demonstrates the opposite The writers' own study is not a trial and while the results are commendable does not contribute to the controversy.

We believe that the practice of placing a drain after simple cholecystectomy is completely unnecessary and have not done so for 4 years without regret.

Z. Raytor
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Totally stapled abdominal restorative proctocolectomy

Sir

We have been interested in the recent paper by Kmiot and Keighley[1] describing a 'totally stapled' procedure for restorative coloproctectomy (*Br J Surg* 1989; 76: 961–4) which seems a reasonable alternative[2].

Difficulties are frequent in performing the linear transection at the anorectal junction from the abdomen: as outlined in the series from Birmingham, two male patients with megarectum were unsuitable for this technical step, leading to conventional manual transanal pouch anastomosis.

In such cases, the technique we developed may be beneficial (*Figure 1*). Using the eversion technique[3,4], the linear stapled transection of the rectum is perforated by the perineal route, after identical abdominal mobilization of the rectum. The same technique may be performed for isolated rectal resection followed by colonic pouch anastomosis. Experimental studies have confirmed the feasibility and safety of the procedure performed successfully in six restorative coloproctectomies from January 1989[5].

P. A. Lehur
J. Leborgne

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France

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2. Williams NS. Restorative proctocolectomy is the first choice elective surgical treatment for ulcerative colitis. *Br J Surg* 1989; **76**: 1109–10.
3. Goligher JC. Eversion technique for distal mucosal proctectomy in ulcerative colitis: a preliminary report. *Br J Surg* 1984; **71**: 26–8.
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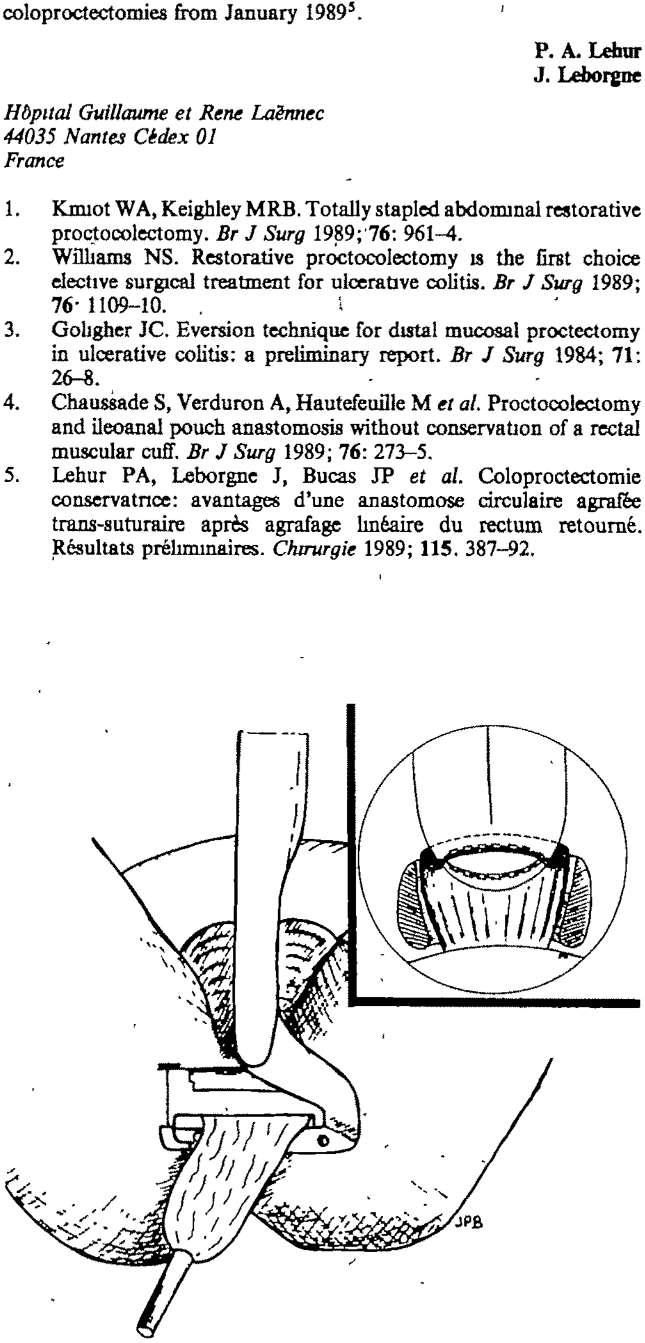

Figure 1 *Linear stapled transection at the anorectal junction after eversion, perineal route. Inset: completed circular inverted pouch–anal anastomosis, with laterally inverted linear stapled closure of the upper anal canal*

Conservative treatment of ingrowing toenails

Sir

We read with interest the article 'Conservative treatment of ingrowing toenails' by Reijnen and Goris (*Br J Surg* 1989; 76: 955–7). We acknowledge that a period of conservative treatment should be considered before surgical intervention; yet is it necessary for patients to endure such prolonged suffering for very little reward?

The absence of an alternative treatment group, such as simple nail edge packing or gutter insertion and the heterogeneous nature of the patient population combine to make this a poorly designed study. Eleven doctors undertook conservative treatment on only an average of 11 nails but each individual's performance is not specified. The authors claim that their treatment is 'time consuming' but fail to report how long each primary treatment took. As patients were not reviewed independently, an unbiased, objective assessment cannot be made. The results of conservative management in the 30 patients who had previously undergone toenail surgery, and therefore demonstrated resistance to previous treatments, have been omitted.

The 'conservative' technique in itself appears to border on the barbaric. Analgesia requirements and the amount of pain suffered by each patient during this procedure are not stated. We suspect that lifting embedded nail edges out of the nail fold and filing the central portion of an ingrowing nail would be extremely distressing for the majority of patients if no analgesia was administered. Furthermore, 31 nails (26 per cent) ruptured as a result of filing. This morbidity is excessive and unacceptable.

Nail edge excision and phenolization under digital block anaesthesia in our experience can be completed in 15 min and has a recurrence rate of <10 per cent at one-year review[1]. The cosmetic results are satisfactory and the treatment is not attended by the complication of nail rupture.

Reijnen and Goris' proposed technique has not been shown to be superior to conventional methods of conservative treatment and cannot be justified in ingrowing toenail management.

J. H. Anderson
J. D. Greig
J. R. Anderson

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Glasgow G31 2ER
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1 Greig JD, Anderson JH, Ireland AJ, Anderson JR. Prospective randomized study of ingrowing toenail management. *Br J Surg* 1989; **76**: 1335.

Authors' reply

Sir

We would like to comment on the remarks of Mr J. H. Anderson *et al* point by point.

Our study was started because the literature furnishes little information on the conservative treatment of ingrown toenails. The aim was to establish the value of this specific approach in different stages of ingrown toenail. We did not intend to prove its superiority to another method. Our study clarifies that by using this initial approach an important proportion of patients is cured completely. We do not consider a 94 per cent cure rate after 1 month, nor an 84 per cent cure rate after 1 year in stage I and II ingrown toenail 'very little reward'. We recommend a conservative approach for stage I and II only.

We consider it an advantage of our study that this success was achieved by 11 doctors following a fixed protocol. It reflects the practical value of this approach.

In our opinion the number of (check) visits justifies the use of the term 'time consuming' although primary treatment takes up to 15 min, at its maximum.

We would like to point out that about 90 per cent of all patients were reviewed by an independent assessor.

As a matter of fact the (bad) results in the 30 patients, previously treated surgically, are described in the fifth paragraph of the Results and stressed in the Discussion.

Every rupture, even of less than 0·5 cm length, was recorded reflecting the conscientious search for even the slightest discomfort. The term 'excessive and unacceptable morbidity' seems therefore exaggerated.

We suspect a serious misunderstanding on the side of Mr Anderson *et al* with regard to the (prolonged) suffering of our patients. Packing the nail edge is a little painful but no patient asked for any form of analgesia. In fact, this part of the treatment results in a quick and complete relief of pain. Finally, the torturers of the Barbarians have always known that the sensory nerve endings are localized underneath the nail and not in or on top of the nail, in short, filing the central portion of the nail is not painful.

J. A. M. Reijnen
R. J. A. Goris

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Dilatation of peptic pyloric stenosis

Sir

The stenosis of peptic pyrolic stenosis is more commonly due to inflammation and oedema than fibrosis and scarring. H_2-blockers usually resolve the problem within a week or two and it would be interesting to know if the single balloon dilatation used by Griffin and his colleagues (*Br J Surg* 1989; 76: 1147–8) would have had more than a temporary effect if the patients had not also been on medical treatment.

T. Bates

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Authors' reply

Sir

We thank Mr Bates for his comments. The relative contribution of oedema and fibrosis to gastric outlet obstruction is conjectural. Our patients had conservative treatment (nasogastric suction, intravenous H_2-blockers) for up to 10 days before the procedure. We were unable to negotiate a fine bore endoscope (Olympus GIF-XQ) through the stenotic area in any of the patients. This suggests that the obstruction is unlikely to be due to oedema alone. Our previous experience is that these patients respond poorly to further prolonged conservation management.

Balloon dilatation only relieves the gastric outlet obstruction. Unlike ulcer surgery it does not influence the ulcer diathesis. Aggressive medical therapy is therefore mandatory in these patients after balloon dilatation. We agree with Mr Bates that without H_2-blocker treatment, the benefit of balloon dilatation is likely to be short-lived as recurrent ulceration would cause further scarring and retenosis.

A. K. C. Li
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Book reviews

Atlas of Liver and Biliary Surgery

R. Scott Jones. 285 × 220 mm. Pp. 307. Illustrated by C. A. Luce. 1990. Chicago: Year Book Medical. £49.00.

The realm of complex hepatobiliary surgery is one in which only a small minority of surgeons can expect to gain any meaningful experience during their training. This book has been written for surgeons in training. In essence it consists of a well illustrated description of operative detail and strategy. After a general introductory section there are three sections dealing respectively with liver surgery, biliary surgery and a selection of techniques useful in the management of portal hypertension. The technical details are heavily supported by high quality line drawings. The American origin of the book is reflected in both literary and operating style.

Generally this is a good book which goes on a long way to achieving its aim. The author readily accepts as inevitable that surgeons with an interest in this area will quibble with certain of the recommendations. I was a little disappointed in the way that certain key portions of complex procedures were portrayed. For example the approach to the location and control of the vasculature of the medial segment of the left lobe (segment IV) of the liver during extended right hepatic lobectomy was inaccurate and misleading. The description of a high Roux-en-Y hepaticojejunostomy looked good on paper but if attempted as described considerable difficulty can be encountered in accurately placing the last few sutures.

The text is well written and easy to read although the dogmatic way that certain points of operative detail and postoperative management were specified was irritating. There could have been more detail on the surgical relevance and management of certan biliary and vascular anomalies which are not infrequently encountered.

While the book does not claim to be comprehensive it would have been significantly enhanced by a section on liver transplantation and the inclusion of some detail on gastric devascularization, oesophageal transection, approaches to intra-arterial chemotherapy and both diagnostic and therapeutic laparoscopic surgery

Despite these reservations the book is well produced (I noticed only two typographical errors: pages 269 and 270) and represents good value for money. I will watch with interest for further titles in the series.

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and Gartnavel General Hospital, Glasgow G12 0YN
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Principles and Practice of Surgical Pathology. Volumes 1 and 2. 2nd Ed.

S. G Silverberg. 220 × 285 mm. Pp. 2182 (both volumes). Illustrated 1990. New York Churchill Livingstone £150.00.

This is a two volume glossy book produced by a large group of pathologists predominantly from the USA Each volume has more than 1000 pages and each chapter has a copious reference list. The references to most chapters seem to be basically from the American literature and in some exclusively so The books are beautifully produced with very clear illustrations. The quality of the paper makes each volume extremely heavy which I find a significant disadvantage

As in all multi-author books, the standards vary and whilst much of the descriptive writing on histopathology is excellent and well illustrated I find a number of the clinical comments sketchy and dated. There is no doubt this is an encyclopaedic book full of information covering the whole field of surgical pathology. It is strongly slanted towards the pathologist so it may find its way into the library of hospital pathology departments but it is not a book that surgeons will buy or read.

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Intraoperative Ultrasonography in Hepato-Biliary and Pancreatic Surgery. A Practical Guide

G. Gozzetti, A. Mozziotti, L. Bolondi and L. Barbara. 165 × 245 mm Pp. 184. Illustrated. 1989. Dordrecht, The Netherlands: Kluwer Academic Publishers. £60.00.

British surgeons were late to appreciate the value of intraoperative ultrasound, lagging behind European surgeons some of whom have been pioneers in the field. The technique has undoubtedly revolutionized liver and pancreatic surgery and the publication of this book is well timed to coincide with the increasing British interest in the technique.

The early chapters contain a brief résumé of the physics involved, the development of ultrasound and the various types of instrument that are available. The use and indications for the different types of probes are explained This section was easy to understand and I found it very helpful The remainder of the book covers the various applications of intraoperative ultrasound. The largest chapter concerns its role in hepatic surgery. The appearance of common pathological conditions is shown and it describes how the technique facilitates hepatic resection including segmental resection for carcinoma. I was a little disappointed that its role in delineating the segmental anatomy of the liver was not emphasized as I believe this understanding is fundamental to hepatic resection. A brief description of the use of intraoperative ultrasound in other conditions such as hydatid disease, pyogenic abscess, trauma and benign tumours is included. Subsequent chapters cover the extensive use of intraoperative ultrasound in surgery of the bile ducts and calculus disease, its use in pancreatic surgery and finally its use in portal hypertension and liver transplantation.

I think that this inexpensive book will be useful for anyone contemplating learning the technique of intraoperative ultrasound. Throughout, it is well illustrated with high quality ultrasound plates linked with line drawings and photographs of pathological specimens were appropriate. The quality of the illustrations is a particularly attractive feature of the book. Though small, it gives an excellent overview of the subject and I think that it will be stimulating to those who read it.

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Sir James Paget: The Rise of Clinical Surgery

S Roberts. 240 × 152 mm. Pp. 197. Illustrated. 1990. London Royal Society of Medicine. £12 95 hardback, £7.95 softback

The first thing to understand about this book is that it is neither a lightweight historical novel nor a medical treatise. it is a serious biography of one of our greatest surgeons. A medical education is not required to appreciate the book, although an interest in medicine or – more exactly – the history of medicine, helps.

Paget was born in 1814 and his life is chronicled from his childhood in Great Yarmouth through his professional career in London to his death in 1899. The book is enlivened by considerable quotations from the letters and papers of Paget, and from those of his family and contemporaries. The author guides us gently between this quoted text with a style and professionalism which gave this reader great pleasure. In the 223 pages there are 33 illustrations which integrate well with the text and are attractive to the eye. My only complaint about the volume is its greyish cover which makes it look rather forbidding

In the end, whether this book is read by surgeons will depend on their attitudes to our medical past It is to be hoped, in our headlong rush toward future scientific advance, that we do not lose track of our history, or of the professional integrity which Paget displayed so well Surgeons will come to no harm by reading this book

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Cancer of the Head and Neck. 2nd Ed.

E. N Myers, J Y. Suen 265 × 210 mm Pp. 1132 Illustrated. 1989. New York Churchill Livingstone £95 00.

In 1982 Ian McGregor reviewed the first edition of *Cancer of the Head and Neck* for *The British Journal of Plastic Surgery*. The first Edition was edited by James Y. Suen and Eugene N. Myers, there has been a change of order. McGregor commended the book but felt that there were weaknesses in the areas of reconstruction and challenging clinical problems.

The 40 chapters comprehensively cover the whole field of head and neck oncology. There are 60 contributors to this volume, all but two being from within the USA The varying tumour types and their sites of occurrence are discussed in each chapter The chapters have a regular format incidence, epidemiology and etiology, anatomy, patterns of spread, classification and staging, pathology, prognostic features, diagnostic studies, clinical features and management and, the complications. In most of the chapters the section on repair following the surgical ablation of the tumour is brief This must be a major criticism in an age where restoration of function and cosmesis are of major importance in the total patient management The chapter on the reconstruction of major head and neck defects is barely acceptable. Although the majority of the available flaps are included the line drawings are inaccurate, the surgical descriptions brief and there is little mention of complications References appear at the end of each chapter, they are comprehensive and accurate. The index fulfils its role adequately

It may be that the editors have been over-ambitious in trying to cover the field of head and neck surgery in one book Areas of the complete management of our patients must suffer. There is no doubt in this tome the surgical approach and reconstruction receive the barest of attention. Ian McGregor in 1982 felt that the first edition would get the reader through his American Boards and answer an MCQ examination. The second edition will achieve equal results Maybe the editors have targeted this audience

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Pancreatitis

D C Carter, A. L. Warshaw 255 × 200 mm Pp. 189 Illustrated. 1989. Edinburgh Churchill Livingstone £30.00

The Clinical Surgery International series has as its aim the in-depth study of current areas of interest in surgery This, the sixteenth, has been produced under the editorial guidance of Professor David Carter and Dr Andrew Warshaw who have enlisted the help of a strong group of American and European experts.

The volume opens with a review of the pathogenesis of pancreatitis. This is thorough and up-to-date although the conclusion is still that 'the pathogenesis of acute pancreatitis remains largely unknown'. The following six chapters on acute pancreatitis follow a logical sequence and discuss the problems of the moment I found Berger's chapter on pancreatic abscess disappointing as it describes the Ulm group's strategy but fails to discuss the pros and cons of other options such as laparostomy The remainder of the book concerns chronic pancreatitis reviewing medical as well as surgical options

The main irritation of this book is the need of many authors to define what they were discussing Some quote the Cambridge meeting, others Marseilles. An opening editorial chapter achieving a consensus on this point would have been helpful and led to more precision Many chapters refer to biochemical parameters using a variety of results; could they not have standardized on SI units?

Overall this is a useful volume and at £30.00 not too expensive It would make a useful addition to any surgical library

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Common Problems in Vascular Surgery

D Brewster. 230 × 155 mm. Pp. 469 Illustrated. 1989 London Wolfe Medical £37.50.

This book was published in 1989, as part of a series '*Common Problems in Surgery*' which already contains other volumes concerning endocrine, gastrointestinal, surgical oncology and trauma. A comprehensive list of problems in arterial and venous surgery is discussed by a large number of eminent contributors, all but one of whom are from North America The format used is unusual, in that each author has been presented with a short clinical problem and is then asked to describe his preferred course of management. This makes an entertaining book, which is highly readable, but one aspect of its design is very irritating, each author has been asked to give some references at the end of each chapter which he considers suitable for further reading, but the statements which he makes in the text are not related, in general, to those references, so it does not enable the student to follow-up his line of argument without reading the whole list of references which the author has given. There is also a predictable tendency towards aggressive surgical interference running through the whole book and I had a feeling that the case against surgical intervention was laid with less enthusiasm than that for operation This lack of balance detracts considerably from the ultimate value of the work and will, I am afraid, reduce its credibility amongst physicians as opposed to surgeons

It is always extremely difficult to cull good evidence from the published literature to support our day to day management of patients Management is coloured by our own personal prejudices and experiences and we sway from the conservative to the aggressive on recent personal results There is, in the sub-speciality of vascular surgery, a particular lack of controlled clinical trials, which is typical of this somewhat immature branch of surgery. There are, however, welcome signs that this sad deficiency is being rectified and many controlled trials of major problems in vascular surgery are now under way.

I would not wish these comments to detract from the usefulness of this book. It covers a wide variety of subjects which concern and worry all vascular surgeons, the style of authorship is fairly homogenous considering the multiplicity of authors and it is neatly produced, with a good standard of illustration. There is an adequate number of valuable references, although I only wish they had been more accurately documented in the text. I found it a very difficult book to put down.

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Trauma Management

D J. Kreis Jr, G A Gomez. 180 × 260 mm. Pp 542 Illustrated 1989 Boston Little Brown and Co. £69 95

This book contains a very comprehensive review of trauma management The editors and 43 contributors are from centres in the South and East of the USA but this does not significantly detract from the practical value to surgeons elsewhere. Although perhaps of most relevance to surgeons-in-training who are actively involved in the care of trauma victims, parts of the book would be of interest to any surgeons working in this field.

The contents have been well planned and are generally of high quality An informative account is given of the organization of trauma services in North America A series of chapters, occupying about half of the book, deal with trauma to individual body systems Most of these chapters are well written and strike a good balance between reviewing contentious issues and giving sound practical advice. The remainder of the book covers diverse but important topics such as trauma in children, multiple organ failure, blood transfusion and nutrition

The only disappointing aspect of the volume is the variable quality of the illustrations Some of the diagrams and black and white photographs are poor, either in the standard of reproduction or in content. This criticism apart, the book is a valuable addition to the literature on trauma management

G. G. Cooper

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Notices and announcements

16–18 May 1990
Blood Vessel Imaging Using Ultrasound Techniques
Southampton, UK
Information. Mr K. N. Humphries, Blood Vessel Imaging Course, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

17–19 May 1990
The first French Symposium on Hernia Surgery
Nice, France
Information: Dr G Dieudonne, Institut Arnault Tzanck, Avenue du docteur Maurice Donat, 06700 Saint-Laurent Du Var, France

23–26 May 1990
Eighty-First Annual Meeting of the American Association for Cancer Research
Washington DC, USA
Information: American Association for Cancer Research, 330 Market Street, 2nd Floor, Philadelphia, PA 19106, USA

24 May 1990
British Association of Endocrine Surgeons Meeting
London, UK
Information. Mr A. W. Goode, Hon. Secretary, British Association of Endocrine Surgeons, The London Hospital, London E1 1BB, UK

27–29 May 1990
International Symposium: Challenges in Vascular Surgery
Norway
Information: Secretariat, Dept of Vascular Surgery, Aker Hospetal 0514, Oslo 5, Norway

28–31 May 1990
Safety in Medial Prqctice
Denmark
Information. ISPIC Secretariat, Professor M. N. G. Dukes, The University of Copenhagen 21 Blegdamsvej, DK-2100 Copenhagen 0, Denmark

29 May–1 June 1990
Peripheral Vascular Disease
London, UK
Information: The British Council, Courses Department, 65 Davies St, London W1Y 2AA

1 June 1990
Melanoma Study Group Summer Meeting
Leicester, UK
Information: Dr R. Graham-Brown, c/o Postgraduate Centre, Leicester Royal Infirmary, Leicester, UK

3–8 June 1990
Third World Congress on HPB Surgery
London, UK
Information: HPB Congress Secretariat, Congress House, 65 West Drive, Sutton, Surrey SM2 7NB, UK

5–9 June 1990
European Association for Gastroenterology & Endoscopy: European Digestive Disease Week
Vienna, Austria
Information: Mondial Congress, Faulmanngasse 4/11 A-1040 Wien, Austria

8–9 June 1990
3rd Annual Meeting of The Surgical Infection Society
Antwerp, Belgium
Information: Professor A Hubens, University Dept of Surgery, Stuivenberg General Hospital, Lange Beeldekenstraat 267, B-2008 Antwerp, Belgium

11–14 June 1990
Current Techniques in Hepatic and Gastrointestinal Research
London, UK
Information· Judit Ashton, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN

11–14 June 1990
6th International Congress on Breast Diseases
Boston, Massachusetts, USA
Information: 6th International Congress Secretariat, c/o Office of Continuing Education, Tufts University School of Medicine, 136 Harrison Avenue, Box 36, Boston, MA 02111, USA

13–16 June 1990
5th European Symposium on Gastrointestinal Motility
Augsburg, FRG
Information. Professor M. Weinbeck, Dept. of Internal Medicine III, Zentralklinikum, D-8900 Augsburg, FRG

20–23 June 1990
Annual Meeting of The Endocrine Society
Atlanta, Georgia, USA
Information: Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

24–28 June 1990
XIII Biennial Meeting of I.S.U.C.R.S.
Graz, Australia
Information· Miss D. Strauss, Executive Secretariat, c/o Indru T Khubchandani, 1275 S. Cedar Crest Boulevard, Allentown, PA 18103, USA

24–29 June 1990
The 3rd Oxbridge Organ Transplantation Course
Oxford, UK
Information. British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

25–27 June 1990
Three day course in hyperlipidaemia
London, UK
Information. Judit Ashton, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN

5–6 July 1990
Surgical Research Society Meeting
Southampton, UK
Information Mr C. D. Johnson, University Surgical Unit, Centre Block 'F' Level, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK

12–14 July 1990
XVth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–15 July 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

15–21 July 1990
1990 Surgical Updating
Milan, Italy
Information: Segreteria Organizzativa, MGR, Via Servio Tullio, 4-20123 Milano, Italy

22–27 July 1990
FASEB Summer Research Conference 'Physiology and Pathophysiology of the Sphlanchnic Circulation'
Colorado, USA
Information. Federation of American Societies for Experimental Biology, Splanchnic Circulation Conference, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

25–27 July 1990
British Association of Paediatric Surgeons XXXVII Annual International Congress
University of Strathclyde, Glasgow, UK
Information· Miss D. Grant, BAPS Administrative Secretary, Royal College of Surgeons, Nicolson Street, Edinburth EH8 9DW, UK

19–23 August 1990
Recent Advances in Oral Maxillofacial Surgery
Glasgow, UK
Information. Louise Deakin, Courses dept., The British Council, 65 Davies Street, London W1Y 2AA

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong
Information: The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

20–21 September 1990
IV Annual Meeting of the European Society for Vascular Surgery
Rome, Italy
Information: Paolo Fiorani, Department of Vascular Surgery, University of Rome, School of Medicine, Policlinico Umberto 1, 00161 Rome, Italy

23–28 September 1990
Comprehensive Review and Update of What's New In Vascular Surgery
Santa Monica, California, USA
Information: Dr W. S Moore, Professor of Surgery, Section of Vascular Surgery, UCLA School of Medicine, PO Box 24901, Los Angeles, California 90024-0901, USA

2 November 1990
Management of Complications Following Vascular Surgery
Newcastle-upon-Tyne, UK
Information· Mr J Chamberlain, Ward 7 Office, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK

SURGERY

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Mosby

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Diagnosis and management of mesenteric infarction

Mesenteric infarction is currently seen by many as a lethal disease essentially affecting a geriatric population in otherwise poor general condition, a picture that inspires resignation. Almost half the patients are not operable at the time of diagnosis, mostly because of delays in establishing the diagnosis and the presence of serious intercurrent diseases. However, there is a potential for better diagnosis and therapy with improved outcome[1,2]. Unfortunately, no clinical signs or laboratory tests are of specific diagnostic value. Abdominal pain out of proportion to abdominal findings is most suggestive, although many clinical presentations are possible, even the complete absence of pain. Marked leucocytosis is strongly suggestive, although its absence does not rule out the diagnosis. Other tests such as determination of serum alkaline phosphatase, lactate or phosphate levels are rarely helpful. The clinical context is of great importance. Cardiovascular history is found in practically all cases of arterial and nonocclusive infarctions. Previous history of thrombophlebitis, coagulopathy, pulmonary embolism, cirrhosis or pancreatic disease is the rule in infarctions of a venous aetiology[3,4].

When mesenteric infarction is suspected, it is essential to obtain appropriate diagnostic investigations as quickly as possible and the cause of the infarction, whenever possible, should be identified before operation. In this setting, selective arteriography preceded by an aortogram is regarded by most authorities, although not all, as the 'gold standard'. Proximal obstructions of the superior mesenteric artery (SMA) are typically the result of thrombi, while more distal obstructions (e.g. as far as the ileocolic artery) result from emboli. Nonocclusive infarction and venous ischaemia yield less obvious arteriograhic findings. Arterial vasospasm, as well as defects of venous filling, are difficult to demonstrate. Combination of different causes (such as arterial or venous thrombosis with a low flow state) is certainly more frequent than usually recognized. Another advantage of selective arteriography resides in the possibility of inserting a catheter into the SMA, allowing continuous and selective infusion of substances such as vasodilators (e.g. papaverine, phenoxybenzamine or adenosine triphosphate) or thrombolytic drugs. Boley *et al.*[5] championed the technique using papaverine, reporting a dramatic influence on survival and even obviating, in selected cases, the need for laparotomy. It is, however, still unclear whether release of the splanchnic resistance in the SMA, clearly demonstrated to be beneficial in non-occlusive forms of ischaemia and some cases of arterial occlusion, is effective in all forms of mesenteric ischaemia. From a practical point of view, selective vasodilatation requires close monitoring and, when the vasodilator is continuously perfused, observation in an intensive care unit. This may be difficult to obtain for elderly and debilitated patients. Our experience is that selective vasodilatation is at least not deleterious and is probably helpful in some circumstances, and that the catheter can be used for serial arteriography.

As an alternative to selective delivery of medication into the SMA injection of some substances intravenously has been proposed to prevent tissue damage related to ischaemia, vasoconstriction or reperfusion. As with other organs subjected to reperfusion, the intestines sustain damage that appears related to oxygen metabolites such as the superoxide anion, hydrogen peroxide or the hydroxyl radical. Therefore, therapy with free-radical scavengers (e.g. superoxide dismutase or 5-aminosalicylate) or xanthine oxidase inhibitors (e.g. allopurinol, oxypurinol or pterin aldehyde) has potentially beneficial effects. In different experimental models, glucagon has also been found useful by increasing mucosal flow. Prostaglandin E and prostacyclin (PGI_2) increase flow in both the SMA and portal vein in spite of decreases in the systemic blood pressure. Although prostaglandins seem quite selective, most of the substances studied are non-selective, a finding which probably explains the controversial and disappointing results obtained by intravenous mesenteric dilatation. Mesenteric resistance has been recently found to be under control of the renin–angiotensin axis and vasopressin mechanisms, thus yielding new therapeutic horizons with drugs such as captopril, teprotide or saralasin in mesenteric ischaemia. These structurally related peptides, namely corticotropin releasing factor, sauvagine and urotensin I, have been

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found so be highly selective dilators of mesenteric vasculature when given intravenously in dogs and rats. The effect appears to be independent of adrenocorticotrophic hormone or cortisol release. However, convincing data in humans are still lacking and data from animal models show that some of these drugs are effective only when injected before ischaemia, a major limitation for the clinical application of these agents.

Mesenteric venous ischaemia is a distinct entity and has a better prognosis than other forms of infarction[3,4]. Contrast-enhanced computed tomographic scanning appears to be the diagnostic method of choice and may show reduced contrast density in the superior mesenteric vein with or without portal thrombosis, dilated intestinal loops with massive wall dilatation, and the presence of peritoneal fluid[6]. The latter finding seems to correlate with the degree of reversibility of the ischaemia. We recently suggested that, in the absence of ascites, conservative therapy with intravenous heparin in therapeutic doses can be attempted[7]. In addition, in patients with liver cirrhosis, conservative treatment should, in our opinion, be used if paracentesis does not recover serosanguineous fluid.

Prompt laparotomy is mandatory on suspicion of mesenteric ischaemia with the exception of selected cases of venous ischaemia[6,7] and, perhaps, when there is clear relief of symptoms with selective vasodilator perfusion[5] or after percutaneous transluminal angioplasty in patients with a short and single proximal obstruction of the SMA[8]. Whether revascularization should be attempted and how much intestine has to be resected is often difficult to evaluate. In case of embolization of the SMA a catheter embolectomy is indicated before bowel resection unless the obstruction is very distal. Access to the SMA is obtained at the root of the small bowel mesentery as proximally as possible, usually at the level of the ligament of Treitz. A balloon catheter is introduced through a longitudinal arteriotomy. When there is doubt about residual narrowing, a patch (venous graft by preference) is justified[9]. However, a sufficiently proximal opening of the SMA allows successful closure using fine suture technique without a patch. Proximal obstructions require bypass procedures. Long-term results may depend on the number of bypasses used and the number of vessels revascularized. As opposed to catheter embolectomy, mesenteric bypass surgery is a specialized operation and should only be attempted by surgeons with extensive experience. In venous infarctions, thrombectomy removes only thrombi localized in large venous trunks and perpetuates ischaemia by leaving the obstruction in small veins in the vicinity of the bowel[3,4]. Furthermore, in animal experiments, residual intense arterial spasm has been found after removing the venous occlusion[10]. Therefore, revascularization of larger veins by thrombectomy, although occasionally reported, is not to be recommended.

How much intestine should be removed? Visual appreciation of bowel damage based on capillary bleeding, colour and contractility is often misleading and commonly leads to more extensive resection than is necessary. Numerous methods of assessing the viability of the intestine have been clinically and experimentally tested in the last decade, but only Doppler ultrasound and dye methods (e.g. fluorescein injections and observation by the Woods lamp) are currently used. Approaches aimed at evaluating metabolic phenomena directly (e.g. mucosal permeability measures or myoelectric wall activity) or indirectly (e.g. measurement of pH, P_{O_2} and P_{CO_2}) offer promise. Laser Doppler flowmetry, surface temperature measurement, and plethysmography represent other valuable lines of enquiry in assessing flow. Finally, surface oximetry or surface tonometry are elegant indirect measurements of oxygenation and pH and therefore of metabolic activity. Refinements and prospective clinical comparative studies of these methods will probably change the way of assessing bowel viability in the near future.

Only bowel which is clearly the seat of transmural necrosis should be resected. Preservation of bowel length is important if we are to avoid nutritionally crippled survivors. However, in venous infarction, the recurrence rate is high and is largely due to residual thrombi at the resection lines[3,4]. Since the length of ischaemic bowel is usually limited, an extensive intestinal resection, using resection lines some 10 cm away from the ischaemic segment, is to be recommended in venous ischaemia[4]. For all types of infarction, if doubt about bowel viability remains, a second look within the next 24 h or laparostomy should be undertaken.

Anticoagulation therapy should be used in all forms of mesenteric infarctions, but the type of anticoagulant and the duration of therapy remain speculative. We begin during operation by giving dextran 50 (40 g/day) or intravenous heparin, attaining therapeutic doses over 24 to 36 h. Both drugs are replaced by coumarin when the patient resumes oral feeding. The anticoagulation is usually maintained over 3 to 6 months. In the presence of a hereditary deficiency in a coagulation factor such as antithrombin III, protein C or S (all are routinely assessed), anticoagulation is used indefinitely.

Today, it is no longer acceptable to abandon all investigative procedures on the suspicion of mesenteric infarction. Assessment of the patient's general condition on admission is often misleading and surprising results are often obtained by using an aggressive diagnostic and therapeutic approach. At the very least, the cause of the ischaemia as well as the extent of the necrotic gut has to be defined to make appropriate decisions regarding curative or supportive treatment.

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Management of severe acute cholangitis

Despite an adequate trial of antibiotic therapy, biliary sepsis fails to resolve in 15 to 30 per cent of patients with cholangitis[1,2]. In the past, surgery was the only effective form of treatment for patients with severe acute cholangitis but it carried a high postoperative morbidity and mortality rate[1,3,4]. A number of recent reports, including our own, have supported the view that endoscopic biliary drainage may be a useful method of treatment particularly for patients with calculous cholangitis[2,3,5]. As the dominant role of surgery in the management of these patients with fulminating biliary sepsis is challenged by the remarkable results achieved by the endoscopists, a closer look at the issue is mandatory. Percutaneous transhepatic biliary drainage probably has a limited role in the treatment of calculous cholangitis as subsequent therapeutic measures can be better provided by endoscopic means and the approach is therefore omitted from the present discussion. Patients with malignant obstruction should also be considered separately as, although sepsis occurs infrequently, if direct cholangiography is avoided[6,7], it carries a significantly worse prognosis.

At the time of emergency endoscopy, complete endoscopic sphincterotomy followed by ductal clearance with active instrumental stone extraction is probably the best way to secure biliary drainage. Adoption of such an aggressive endoscopic approach should, however, be reserved for selected patients with simple ductal pathology. In patients with multiple common duct stones, including large ones which require mechanical fragmentation, complete ductal clearance is not necessary to establish satisfactory biliary decompression. Effective control of severe acute cholangitis can be accomplished by the introduction of a 7 Fr nasobiliary catheter proximal to the site of obstruction and is associated with negligible procedure related complications. In our last 40 consecutive patients managed by endoscopic nasobiliary drainage undertaken by one individual, sepsis resolved with rapidity equal to that achieved by surgical drainage with a larger T tube despite the presence of residual stones and, on many occasions, incomplete endoscopic sphincterotomy. In experienced hands, the entire procedure of endoscopic sphincterotomy and nasobiliary catheter insertion can be concluded within 30 min. A lengthy endoscopic procedure to obtain complete ductal clearance, even under local pharyngeal anaesthesia, is potentially hazardous for these critically ill patients.

Improvement in overall morbidity, including that of the initial endoscopic drainage and subsequent surgical ductal clearance, is however less remarkable when compared with the results of definitive emergency surgery alone[5]. Moreover, the potential ability to reduce the mortality rate associated with severe acute cholangitis by therapeutic endoscopy deserves further examination. Based on the data of 86 consecutive patients in our unit who had surgery for fulminant calculous cholangitis, five independent risk factors were identified on multivariate analysis[3]. These were the presence of concomitant medical problems, arterial blood pH $<7{\cdot}4$, total serum bilirubin level more than 90 μmol/l, platelet count less than 150×10^9/l and serum albumin concentration less than 30 g/l. In patients with two or fewer of these risk factors, the mortality rate of emergency surgery was 6 per cent which compared favourably with that of therapeutic endoscopy.

From currently available data, it would appear that all patients who have severe acute cholangitis should undergo an emergency endoscopic retrograde cholangiogram to define the exact ductal pathology. An immediate decision regarding the appropriate method of biliary drainage to be initiated can then be made according to the cholangiographic findings. In the presence of common duct stones endoscopic drainage, at least as an initial measure, is advisable for patients considered to have high operative risk (three or more risk factors), and those who have previously undergone cholecystectomy. For patients with two or fewer risk factors, emergency definitive surgery should be considered for those who have gallstones as the benefit of initial endoscopic decompression is not clearly evident at present. In Hong Kong and elsewhere in Asia, patients with complicated intrahepatic calculi and/or strictures are not infrequently encountered. Although attempts at initial endoscopic drainage for such patients are occasionally worthwhile, surgical correction is preferred as satisfactory endoscopic decompression is often difficult to achieve.

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As most published data are either retrospective or prospective but uncontrolled in nature, conclusions regarding the value of therapeutic endoscopy should be taken with some reservation. There remain doubts as to the effectiveness of endoscopic sphincterotomy and nasobiliary drainage for the management of patients with thick purulent bile, especially in the presence of residual ductal stones. Furthermore, the results of emergency endoscopic decompression should be analysed with proper stratification of patients according to operative risk. A randomized control study is the only means to determine the value of emergency endoscopic drainage for patients with severe acute cholangitis. Since November 1987, a total of 55 patients have been enrolled in an ongoing prospective trial in our department and have been randomized to undergo emergency surgery or initial endoscopic drainage. Hopefully, the data obtained will resolve some of the uncertainties about therapeutic endoscopy and define more precisely the role of surgery and endoscopy in the management of patients with severe calculous cholangitis.

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Interaction of penetrating missiles with tissues: some common misapprehensions and implications for wound management

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It is apparent from review of published papers and books that misunderstanding and confusion exists in the minds of many authors describing the interaction of penetrating missiles with tissues. These misapprehensions may influence the management of wounds by suggesting didactic approaches based upon a preconceived notion of the nature and severity of the wound for different types of projectiles. This review considers the biophysics of penetrating missile wounds, highlights some of the more common misconceptions and seeks to reconcile the conflicting and confusing management doctrines that are promulgated in the literature – differences that arise not only from two scenarios, peace and war, but also from misapprehensions of the wounding process. Wounds of war and of peacetime differ both in the nature of the wound and in the propensity for wound infection. Additionally, the limitations imposed by war dictate the type of management that may be practised and result in procedures that would be considered inappropriate by some in civilian clinical practice. Many of the procedures described in civilian peacetime settings, such as reliance on antibiotics alone for the control of infection in penetrating wounds, or minimal excision and debridement, can yield good results but would herald disaster if transposed to a war setting.

Keywords: Wound, penetrating, ballistics, debridement, wound infection

Perusal of nearly any textbook on trauma containing descriptions of the interaction of missiles with tissues reveals some common misconceptions about the relationship between the kinetic characteristics of the missile and the severity of the wound. Foremost amongst these is the role of impact velocity in determining the severity of a wound and the extent of indirect injury away from the track of the projectile resulting from 'high velocity' projectiles passing through soft tissue. These misconceptions may actually influence management of a wound in that there may be preconceived notions about wound severity in the light of presumed or actual knowledge of the type of wounding missile and generalizations regarding the characteristics of a wound.

Management doctrines must be influenced by the facilities available for surgery and postoperative care. The emphasis in most textbooks is upon management within a civilian clinical setting in peacetime. War imposes significant limitations on the type of surgery that may be practised (particularly in forward areas) and in the scale and nature of postoperative care that may be required during evacuation. Additionally, the type and severity of wound differs in many respects from those seen in the civilian setting, notably with respect to the greater potential for infection within the military wound.

The purpose of this paper is to review the biophysical aspects of the interaction between penetrating missiles and soft tissue and bone. Additionally, we identify general aspects of management of wounds that are specifically influenced by the conditions pertaining to war.

Interactions of penetrating missiles with tissues

Penetrating missiles, for practical purposes, can be classified into two major groups, fragments and bullets. Fragments are the most common wounding agents in war, accounting for between 44 and 92 per cent of all surgical cases during recent campaigns[1]. Antipersonnel fragments from military munitions tend to be small and numerous to achieve a high probability of a hit, and to be fairly regular in shape to ensure adequate range and consistent performance. In civilian clinical practice, bullets are the predominant penetrating missiles although fragmentation injury occurs following terrorist bombings; these fragments usually originate from the environment within which the bomb explodes, tend to be irregularly shaped and have a wide range of masses and impact velocities. It is appropriate to differentiate initially between the behaviour of small, relatively uniform, projectiles such as antipersonnel fragments and the behaviour of bullets. The long, cylindrical shape of bullets influences the rate at which energy is transferred to a target and can result in a different pattern of injury along the wound track compared with that produced by fragments.

Most military antipersonnel fragments have poor penetrating power and limited effective range. They have low mass and ragged edges; consequently the drag on the projectile in air and particularly in soft tissue is high. The mechanical injury in casualties surviving to reach surgical facilities may be quite modest. However, many have multiple wounds, heavily

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have little clinical significance in the management of penetrating wounds in humans. They can occasionally be demonstrated as petechial haemorrhages in animal models.

The strain or instability within the soft tissue surrounding the cavity may actually produce sufficient force to cause indirect fracture of a long bone: a bullet resulting in high energy-transfer need not strike bone to fracture it. Stress waves may also be implicated in indirect long bone fracture.

The sizes of missile entry and exit holes are governed by the size and shape of the penetrating missile and the degree of energy-transfer at the site. The formation of a large temporary cavity at either site invariably results in gross soft tissue injury and the skin may exhibit stellate lacerations. Although a large tissue defect is quite obviously the result of large energy-transfers or missile fragmentation, the corollary that small entry and exit wounds imply low energy-transfer is not true; high energy-transfer may have occurred internally This is particularly true of long wound tracks such as abdominal wounds where significant yaw and energy-transfer may occur within the abdominal cavity and result in serious injury to viscera, although the projectile may retain little energy in the distal parts of the track and produce a small exit wound or may remain lodged in the tissues.

Wound contamination

The dispersal of wound contaminants by the temporary cavity is underestimated. The contamination is a notable problem in military wounds where there is high available energy and has major implications for the control of wound infection. Fragments and any other projectiles with sharp, irregular surfaces transfer notable quantities of skin and clothing material into wounds. With low velocity projectiles, the clothing tends to be a ragged piece At increasing impact velocity, clothing is shredded and, if a temporary cavity is formed by the projectile, fibres and large pieces of material may be dispersed radial to the missile track and may result in contamination of tissues and fascial planes where there is no evidence of physical injury.

Most bullets are pointed and transfer little material from the entry site but if a temporary cavity involves the exit wound, substantial quantities of material may be sucked into the wound from the exit hole, creating widespread contamination and potential for infection at multiple sites. Wound debridement and excision therefore have a role additional to the removal of non-viable tissue, namely, the removal of visible contaminants. This may involve the excision of viable but heavily contaminated soft tissue.

Bullet fragmentation

A possible consequence of the changes in presented area as a bullet yaws within soft tissue is break-up or deformation, the pathophysiological sequelae may be devastating Military bullets comprise lead and steel components clad within a metal jacket. If jacketed bullets do disrupt, it is usually by extruding lead from their base as a result of distortion of the jacket induced by high forces during yaw. This is particularly pronounced at very short range (less than 50 m) when not only is the available energy high, but also bullets are relatively unstable and may strike with a yaw of 3–5°. As a consequence of this small but significant yaw in air, the yaw cycle may be induced immediately upon entering soft tissue resulting in excessively high forces on the jacket with the risk of distortion or break-up.

The tendency to break-up is governed by the construction of the bullet, principally the thickness of the jacket and the efficiency of the base in preventing extrusion. Some bullets for police use and for hunting are designed to fragment but the Hague Declaration of 1899 ruled that such bullets should not be used in armed conflicts.

The disruption of a bullet into small pieces produces irregular fragments which result in high retarding forces and the transfer of larger quantities of energy. The resulting large temporary cavity will be associated with multiple, diverging wound tracks. One clinical result is multiple laceration of the tissue surrounding the original wound track, and although one may argue about the role of the temporary cavity in rendering tissues non-viable, there can be no argument about rapidly moving pieces of metal disrupting and lacerating tissue.

Another interaction that may involve disruption is contact with hard, high density bone. Retardation forces are high and energy-transfer is increased. Fragmented bone provides a large number of secondary fragments which may combine with bullet fragmentation to produce widespread soft tissue disruption in the vicinity of the bone. The impact of any high available-energy projectile upon compact bone will invariably result in bullet fragmentation and more serious wounds, not only due to the fracture itself but also due to injury to blood vessels, nerves and other soft tissue.

The effect of tissue density upon the transfer of energy is also significant in the lung. The lung has a specific gravity of 0·2–0·3 and produces modest retardation to high available-energy projectiles. Little energy-transfer occurs, and temporary cavities are small. Lung is a very elastic tissue and can accommodate temporary cavities with minimal parenchymal injury. The consequence is that nearly all wounds to the lung can be classed as low energy-transfer and thus even high velocity rifle bullet wounds to lung alone carry a low mortality rate, the principal threat being haemopneumothorax.

Although the temporary cavities produced in materials such as gelatin are spectacular with long 'wound' tracks, many wound tracks within human bodies, particularly those involving the limbs, are quite short. Short wound tracks involving soft tissue alone may retard stable bullets very little by failing to induce significant yaw within their short length (*Figures 2* and *3*). A good example is the self-inflicted wound to the foot. At point-blank range the bullet from a rifle has relatively high yaw but even so does not change orientation significantly within the 2–3 cm track and results in a low energy-transfer wound.

Aspects of treatment

'Treat the wound not the weapon' is an apt aphorism that emphasizes that there should be few presumptions when faced with a missile entry and exit wound; knowledge of the wounding weapon occasionally offers insight into wound pathology but should not be seen as the determinant of wound severity. High velocity rifle bullets may produce low energy-transfer wounds, although with many wound tracks in the human body, interaction with bone or long wound tracks can occur and result in high energy-transfers. Although low velocity hand gun bullets often produce low energy-transfer wounds, their projectiles may be designed to deposit all their available energy with a short wound track at the expense of penetration, resulting in the production of relatively superficial high energy-transfer wounds.

Because of factors unique to either battle or peacetime, it is difficult to formulate a management approach that will meet both civilian and military needs. The Defence Medical Services in the UK have developed protocols for penetrating wound management in war and these have been equally influenced by battlefield experience and research. The approach is based on the recommendations of the Inter-Allied Conference held in 1917. By this stage of the First World War, allied surgeons generally agreed that the approach to be adopted for all ballistic wounds should consist of debridement, wound excision and delayed primary closure at 4–5 days after primary surgery.

Critics of this approach regard it as didactic and insulting as it deprives the surgeon of his or her own valued judgement. This may be true but, for general war, departure from this surgical approach has repeatedly resulted in disaster[13–15]. The reasons for these disasters are not entirely clear; experienced civilian surgeons seem consistently to underestimate the pathophysiological consequences of ballistic injury, particularly in the military environment. Odling-Smee relates this point in chilling detail[13]. A further factor is the success of minimal surgery and primary closure of ballistic wounds in the ideal clinical setting of a late 20th century general hospital. Such wounds are usually single, caused by hand gun bullets, and result in minimal contamination. This approach cannot be transferred to the battlefield.

We do not believe that current controversies in the role of wound excision need unduly worry surgeons faced with the management of penetrating missile wounds. The need to excise obviously non-viable soft tissue and muscle is generally agreed. Whether excision should extend to include obviously viable but heavily contaminated tissue is more contentious. Nevertheless, experienced surgeons should have little difficulty if they approach these wounds individually and follow accepted general surgical practice. In the military field-surgical setting, the extent of excision may well be influenced by such factors as delay, early postoperative evacuation, poor conditions and relative inexperience initially with the management of military wounds. It is under these conditions that a tendency towards radical excision is often appropriate. The corollary equally holds. In an ideal clinical setting it may be quite appropriate to lean towards less radical excision; here the patient may be kept under careful review by the operating surgeon and further intervention may be undertaken if appropriate This approach was adopted successfully by Broome and his colleagues after the Hungerford shooting incident[16].

In war the surgeon is faced with unique considerations; these may include delays of 12 h or more from time of wounding to first surgery, wounds heavily contaminated with filthy field clothing and skin fragments, multiple wounds caused by fragments, large numbers of casualties, poor working conditions and staff inexperience. The war wound is, therefore, more than just a physical injury to soft tissue. For management to be effective a great deal of tactical information is required by the surgeon, matters that are rarely of concern in the civil setting.

Wound ballistic science has developed to a stage where a clear understanding exists of the mechanisms involved in the wounding process. It would seem reasonable, therefore, to expect universal agreement on management, such is not the case and the reasons are complex. Increasing urban violence has presented civilian surgeons with large numbers of patients with ballistic wounds. Effective treatment regimens have been developed in large, sophisticated urban hospitals. These regimens have been influenced by the availability of multidisciplinary teams, sophisticated investigative techniques including computerized axial and nuclear magnetic resonance scans, new generation broad spectrum antibiotics (which may be administered within minutes of wounding) and ready access to intensive care units.

This ideal set of circumstances has resulted in the successful use of techniques that would be quite inappropriate on the battlefield. minimal or no surgical intervention for some uncomplicated soft tissue wounds, primary closure of wounds and increasing reliance on antibiotics as the mainstay of treatment[17–19]. It is timely to remind our civilian colleagues that this approach transferred to the battlefield will result in catastrophe for many of the wounded. There are compelling writings of Ogilvie[14] and Odling-Smee[13] as evidence for this view and we entertain the hope that sufficient evidence, both historical and scientific, now exists to prevent repetition of the mistakes of the past.

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Relationship between age and survival in cancer of the colon and rectum with special reference to patients less than 40 years of age

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The relative survival of all patients ($n = 61\,769$) *in the entire Swedish population reported to have a malignant tumour of the colon and rectum between 1960 and 1981 was analysed with special reference to patients under 40 years of age. The 5-year relative survival rate of patients with a tumour of the colon, irrespective of histopathological diagnosis, was 62·0 per cent below the age of 40 years and 44·4 per cent in those 40 years of age or older* ($P < 0{\cdot}05$)*. The corresponding figures for patients with a tumour of the rectum were 46·6 per cent and 39·1 per cent, respectively. When the relative survival was analysed separately for patients with a histopathologically demonstrated adenocarcinoma, the 5-year survival rate among patients with a cancer of the colon was 50·9 per cent in patients below 40 years of age and 48·6 per cent in those 40 years of age or older. In patients with adenocarcinoma of the rectum, the 5-year relative survival rate was 41·1 per cent in patients younger than 40 years of age and 40·7 per cent in patients 40 years of age or older. Thus, patients below the age of 40 years with an adenocarcinoma of the colon and rectum as a group appear to have the same or even a better prognosis than older patients if all tumours are considered, irrespective of histopathological diagnosis.*

Keywords: Colorectal cancer, age, survival

Even in high risk Western populations, adenocarcinoma of the colon and rectum is a rare disease below the age of 40 years; the incidence rate varies between 1·4 and 1·7 per 100 000[1,2]. Children, adolescents and young adults represent only 2·2–7·0 per cent of all patients with colorectal cancer[1–7]. There is considerable uncertainty regarding the prognosis for patients below the age of 40 years. They have been reported to have a worse[3,6–18], a similar[1,2,4,5,19–24] or even a more favourable outcome[25–30] when compared with older patients. The inconsistencies may at least partly be explained by patient selection and random variation due to the small number of cases in many studies (*Table 1*).

The aim of this study was to assess more definitively the survival of patients under the age of 40 years with adenocarcinoma of the colon and rectum by taking advantage of the Swedish National Cancer Registry which provides a large cohort with near-complete follow-up and long-term observation.

Patients and methods

The Swedish Cancer Registry

In Sweden, all cases of malignant tumours have to be reported to the Swedish Cancer Registry, which was started in 1958. Notifications are required from both the responsible clinician and the pathologist or cytologist involved. Ninety-five per cent of all cases are reported by both sources which leads to an almost complete registration with less than a 2 per cent deficit[31,32]. The registry does not contain any information on tumour stage, surgical curability or other clinical data. Dates and causes of death are transferred annually to the cancer registry file by a computerized linkage with the death registry.

Subjects

All patients reported to have a malignant tumour (irrespective of histopathological diagnosis) of the colon (ICD-7 153) or rectum (ICD-7 154) between 1960 and 1981 were retrieved from the cancer registry file. A total of 47 914 patients with malignant tumours of the colon and 26 804 patients with malignant tumours of the rectum had been registered. Cases diagnosed first at autopsy were excluded (8823 cases with a cancer of the colon and 2917 with cancer of the rectum). The number of cases lost to follow-up was negligible (925 cases with colon cancer and 284 with rectal cancer). Left for study were 38 166 patients with a cancer of the colon and 23 603 patients with a cancer of the rectum; in this cohort 1425 individuals (2·3 per cent) were under the age of 40 years. The histopathological diagnoses of all registered tumours are presented in *Table 2*.

Statistical methods

The observed survival (OS) rates from all causes of death were calculated by using the actuarial/life-table method[33]. The relative survival rates were calculated as the ratio between observed and expected survival (ES) rates. The expected survival rate was that for a group of the general population similar to the study group with respect to age, sex and calendar time. A computer program package was used for these calculations[34]. The standard error (s.e.) of the observed survival rate was computed with Greenwood's formula and the s.e. of the relative survival rate was calculated[33] as s.e.(OS)/ES. Ninety-five per cent confidence limits were used. These analyses were made for all malignant diseases reported and selectively for tumours registered as adenocarcinomas.

Results

Age and location

Of all patients with a malignant tumour of the colon and rectum, 1079 (2·8 per cent) and 346 (1·5 per cent) respectively were less than 40 years of age. The anatomical distribution differed between the two age groups; the proportion of rectal tumours was lower below the age of 40 years compared with patients above that age (24·3 and 38·5 per cent respectively). In the colon, left-sided tumours were more common in patients above the age of 40 years whereas tumours of the right colon and the appendix were much more common in younger patients (*Tables 3* and *4*).

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Table 1 *Studies of colorectal adenocarcinoma in young patients*

Study	Age interval (years)	No. of patients	5-year survival rate of young patients (%)	Survival of older patients
Ezzo *et al.* 1958[10]	0–40	33	21	Better
Hall and Coffey 1961[6]	16–40	50	8	Better
Mayo and Pagtalunan 1963[28]	0–30	126	54	Data missing
Miller and Liechty 1967[13]	0–30	33	18	Better
Roth-Mayo *et al.* 1968[23]	20–39	37	32	Same
Rosato *et al.* 1969[25]	0–35	35	43	Same
Recalde *et al.* 1974[11]	0–35	40	13	Better
Sanfelippo and Beahrs 1974[22]	0–40	118	39	Same
Howard *et al.* 1975[21]	18–49	137	31	Same
Scarpa *et al* 1976[26]	20–40	47	37	Worse
Walton *et al.* 1976[4]	0–40	70	41	Same
Vezzoni *et al.* 1977[14]	18–29	28	20	Worse
Simstein *et al.* 1978[12]	0–40	41	28	Better
Mills and Allen 1979[16]	0–30	16	19	Better
Mosley *et al.* 1979[15]	0–30	14	30	Better
Ahlberg *et al.* 1980[35]	0–30	37	41	Data missing
Bulau 1980[1]	0–39	951	32	Same
Bedikian *et al* 1981[7]	0–40	183	25–30	Better
Gardner *et al.* 1981[27]	0–45	32	37	Worse
Martin *et al.* 1981[29]	18–40	37	57	Worse
Safford *et al.* 1981[19]	20–40	120	35	Same
Hsu and Guzman 1982[20]	20–40	18	50	Same
Odone *et al.* 1982[8]	0–20	24	Median 8 months	Better
Öhman 1982[2]	21–39	48	33	Same
Pitluk and Poticha 1983[9]	20–40	31	22	Better
Beckman *et al.* 1984[30]	20–39	69	59	Worse
Moore *et al* 1984[3]	0–40	62	18	Better
Umpleby and Williamson 1984[5]	0–40	85	41	Same
Adloff *et al.* 1986[24]	19–40	32	59	Same
Okuno *et al.* 1987[18]	0–39	57	41	Better
Domergue *et al.* 1988[17]	18–40	78	30	Better
Present study	0–39	958	Men, colon 51 Women, colon 49 Men, rectum 41 Women, rectum 44	Same Same Same Same

Table 2 *Histopathological diagnosis of all registered malignant tumours of the colon and rectum*

	Men		Women	
Histopathological diagnosis	<40 years	≥40 years	<40 years	≥40 years
Colon	494	17 754	585	19 333
Adenocarcinoma	353 (71·5)	15 395 (86·7)	305 (52·1)	16 726 (86·5)
Carcinoid	127 (25·7)	175 (1·0)	266 (45·5)	317 (1·6)
Cancer not specified*	10 (2·0)	2 136 (12·0)	7 (1·2)	2 237 (11·6)
Others†	4 (0·8)	48 (0·3)	7 (1·2)	53 (0·3)
Rectum	175	13 462	171	9 795
Adenocarcinoma	153 (87·4)	12 359 (91·8)	147 (86·0)	8 790 (89·7)
Carcinoid	14 (8·0)	58 (0·4)	17 (9·9)	66 (0·7)
Cancer not specified*	3 (1·7)	882 (6·6)	2 (1·2)	654 (6·7)
Others†	5 (2·9)	163 (1·2)	5 (2·9)	285 (2·9)

Values in parentheses are percentages, * predominantly cases diagnosed without biopsy, † mainly sarcoma, anaplastic cancer, squamous cell carcinoma, malignant melanoma, haemangioendothelioma, lymphangioendothelioma, mixed tumour

Table 3 *Number of cases and 5-year relative survival rate of male patients reported to have a malignant tumour of the colon and rectum by location and age at diagnosis Figures are also presented separately for patients with a histopathological diagnosis of adenocarcinoma*

	<40 years		≥40 years	
Location (ICD-code)	No.	5-year relative survival rate	No	5-year relative survival rate
Ascending colon/caecum (153·0)				
All	158 (32·0)	66·4 (58·7–74·0)	5244 (29·5)	47·4 (45·5–49·3)
Adenocarcinoma	117 (33·1)	55·3 (45·8–64·8)	4623 (30·0)	51·1 (49·0–51·1)
Transverse colon/flexures (153·1)				
All	54 (10·9)	44·4 (30·5–58·3)	2221 (12·5)	44·2 (41·4–47·0)
Adenocarcinoma	52 (14·7)	44·1 (29·9–58·3)	1979 (12·9)	48·2 (45·2–51·3)
Descending colon (153·2)				
All	32 (6·5)	43·3 (24·8–61·7)	955 (5·4)	43·8 (39·4–48·1)
Adenocarcinoma	30 (8·5)	46·3 (27·0–65·6)	841 (5·5)	48·5 (43·8–53·2)
Sigmoid colon (153·3)				
All	90 (18·2)	46·5 (35·6–57·1)	6636 (37·4)	45·1 (43·5–46·8)
Adenocarcinoma	84 (23·8)	48·6 (37·5–60·0)	5895 (38·3)	49·1 (47·3–50·3)
Appendix (153·4)				
All	91 (18·4)	100	145 (0·8)	70·1 (60·0–81·2)
Adenocarcinoma	5 (1·4)	100	87 (0·6)	58·5 (43·3–73·8)
Multiple (153·8)				
All	21 (4·3)	52·8 (31·3–47·3)	357 (2·0)	33·9 (27·5–40·2)
Adenocarcinoma	19 (5·4)	53·0 (30·4–75·7)	279 (1·8)	38·9 (31·6–46·3)
Not specified (153·7, 153·9)				
All	48 (9·7)	49·4 (33·9–64·5)	2196 (12·4)	35·1 (32·4–37·8)
Adenocarcinoma	46 (13·0)	50·1 (35·2–65·9)	1688 (11·0)	42·6 (39·3–45·7)
All colon (153)				
All	494	62·0 (57·5–66·5)	17754	44·4 (43·3–45·3)
Adenocarcinoma	353	50·9 (45·4–56·4)	15392	48·6 (47·5–49·7)
Rectum (154)				
All	175	46·6 (38·6–54·6)	13462	39·1 (38·0–40·2)
Adenocarcinoma	153	41·1 (32·6–49·5)	12359	40·7 (39·6–41·9)

Values in parentheses are percentages and 95 per cent confidence intervals

Histopathological diagnosis

There was a marked difference in the distribution of the histopathological diagnoses in patients younger and older than 40 years (*Tables 3* and *4*). In the younger patients, carcinoids constituted 25·7 per cent of all colon tumours in men and 45·5 per cent in women. Furthermore, 94·9 per cent of the carcinoids of the colon were located in the appendix, the caecum or the ascending colon. In the rectum, carcinoids were slightly more common in patients younger than 40 years of age.

Survival

Analysis of survival including all patients with cancer of the colon showed that patients below the age of 40 years had a significantly better relative survival than older patients (*Table 5*). The survival rates were also analysed for different tumour locations in the colon. Patients younger than 40 years with tumours of the appendix, caecum and ascending colon had a much higher relative survival rate than young patients with tumours in other locations of the colon as well as patients 40 years of age and older (*Tables 3* and *4*). When the survival rates of patients with a histopathological diagnosis of adenocarcinoma were analysed separately, the differences in relative survival rate between tumour locations and age groups disappeared (*Tables 3, 4* and *5*)

The 5-year relative survival rates did not differ significantly between young and old patients with a malignant tumour of the rectum although a tendency towards better prognosis for the young patients was seen (*Tables 3, 4* and *6*). When the survival rates of patients with a histopathological diagnosis of adenocarcinoma were analysed separately, there were no differences between young and old patients.

Discussion

The survival of patients under 40 years of age with colorectal cancer is a matter of controversy (*Table 1*). Most reports have been based on small and more or less selected hospital series, and crude survival rates have often been presented In the present investigation, virtually all patients in the entire Swedish population with colorectal cancer between 1960 and 1981 were analysed The Swedish system with its individual national registration numbers and the availability of computerized registers enabled almost complete follow-up and a possibility of deriving life-tables from the underlying population and of calculating the relative survival. Since this makes adjustments for causes of death other than large bowel cancer, it enables valid comparison between different age groups

In contrast with the opinion that patients below the age of 40 years with colorectal cancer have a worse prognosis than those who are older at diagnosis[3,6,7,9–18], it appears from this study that they have the same or even a better outcome when compared with older patients (*Tables 3, 4, 5* and *6*). Before definite conclusions can be drawn, several factors must be considered, although this finding is in accordance with most large studies carried out previously (*Table 1*).

The anatomical location and the histopathology of tumours differed between patients below and above the age of 40 years. The proportion of tumours of the appendix, caecum and ascending colon was higher in patients younger than 40 years, whereas the proportion of tumours in the sigmoid colon and rectum was higher in older patients (*Tables 3, 4, 5* and *6*). Carcinoids of the colon were much more common in patients below the age of 40 years, whereas the proportion of adenocarcinomas and unspecified tumours was higher in older

Table 4 *Number of cases and 5-year relative survival rate of female patients reported to have a malignant tumour of the colon and rectum by location and age at diagnosis. Figures are also presented separately for patients with a histopathological diagnosis of adenocarcinoma*

	<40 years		≥40 years	
Location (ICD-code)	No.	5-year relative survival rate	No.	5-year relative survival rate
Ascending colon/caecum (153·0)				
All	160 (27·4)	77·8 (71·1–84·5)	6212 (32·1)	48·7 (47·0–50·4)
Adenocarcinoma	81 (26·6)	55·6 (43·6–67·5)	5410 (32·3)	52·1 (50·3–53·9)
Transverse colon/flexures (153·1)				
All	54 (9·2)	40·0 (26·7–53·2)	2542 (13·1)	44·3 (41·8–46·8)
Adenocarcinoma	51 (16·7)	42·4 (28·6–56·2)	2266 (13·5)	48·0 (45·3–50·6)
Descending colon (153·2)				
All	18 (3·1)	49·0 (25·2–72·7)	1087 (5·6)	49·1 (45·3–53·0)
Adenocarcinoma	18 (5·9)	49·0 (25·2–72·7)	982 (5·9)	52·8 (48·4–56·8)
Sigmoid colon (153·3)				
All	91 (15·6)	46·4 (35·5–57·3)	6625 (34·3)	47·1 (45·6–48·7)
Adenocarcimona	89 (29·2)	47·5 (36·4–58·6)	5911 (35·3)	50·6 (49·0–52·2)
Appendix (153·4)				
All	193 (33·0)	97·8 (95·4–100)	217 (1·1)	79·3 (71·9–86·7)
Adenocarcinoma	6 (2·0)	80·4 (45·1–100)	85 (0·5)	61·6 (46·9–76·4)
Multiple (153·8)				
All	15 (2·6)	52·7 (26·9–78·5)	365 (1·9)	40·6 (34·3–46·9)
Adenocarcinoma	13 (4·3)	54·1 (26·8–81·4)	285 (1·7)	49·1 (41·9–56·3)
Not specified (153·7; 153·9)				
All	54 (9·2)	41·7 (27·0–56·3)	2285 (11·8)	35·6 (34·1–39·2)
Adenocarcinoma	47 (15·4)	40·9 (25·5–56·4)	1787 (10·7)	43·2 (40·2–46·2)
All colon (153)				
All	585	70·2 (66·2–74·2)	19333	46·5 (45·6–47·4)
Adenocarcinoma	305	49·0 (43·1–55·0)	16726	50·1 (49·1–51·1)
Rectum (154)				
All	171	50·3 (42·3–58·3)	9795	44·7 (43·4–46·0)
Adenocarcinoma	147	44·5 (36·0–53·1)	8790	46·2 (44·9–47·6)

Values in parentheses are percentages and 95 per cent confidence intervals

Table 5 *Number of cases and 5-year relative survival rate of patients reported to have a malignant tumour of the colon and of cases with a histopathological diagnosis of adenocarcinoma. Figures presented by sex and age at diagnosis*

	Men				Women			
	All		Adenocarcinoma		All		Adenocarcinoma	
Age (years)	No.	5-year relative survival rate	No.	5-year relative survival rate	No.	5-year relative survival rate	No.	5-year relative survival rate
0–9	1*		0		12	100	0	
10–19	51	89·4 (80·2–98·6)	9	44·7 (12·0–77·4)	67	92·7 (85·3–100)	3	33·4 (–86·9)
20–29	132	66·8 (58·4–75·2)	75	46·6 (35·0–58·3)	143	74·4 (66·5–82·1)	49	34·0 (20·3–47·7)
30–39	310	55·6 (49·7–61·4)	269	52·3 (46·1–58·6)	363	63·6 (58·4–68·9)	253	52·3 (45·8–58·9)
<40	494	62·0 (57·5–66·5)	353	50·9 (45·4–56·4)	585	70·2 (66·2–74·2)	305	49·0 (43·1–55·0)
40–49	890	51·0 (47·5–54·5)	799	52·2 (48·5–55·9)	1095	52·3 (49·2–55·5)	948	49·5 (46·1–52·9)
50–59	2455	48·7 (46·5–50·1)	2273	50·3 (48·0–52·6)	2737	49·3 (47·3–51·4)	2510	51·1 (48·9–53·2)
60–69	5190	44·0 (42·3–45·6)	4685	47·7 (45·9–49·4)	5265	46·9 (45·4–48·5)	4818	49·6 (47·9–51·2)
70–79	6402	42·6 (40·8–44·4)	5555	47·7 (45·7–49·7)	6755	44·2 (42·6–45·8)	5874	49·0 (47·2–50·8)
80+	2817	37·7 (34·0–41·3)	2080	49·2 (44·5–53·8)	3481	43·2 (40·1–46·4)	2576	55·0 (51·0–58·9)
≥40	17754	44·4 (43·3–45·3)	15392	48·6 (47·5–49·7)	19333	46·5 (45·6–47·4)	16726	50·1 (49·1–51·1)

Values in parentheses are 95 per cent confidence intervals; * withdrawn

patients (*Table 2*). Since carcinoid tumours carry a more favourable prognosis than adenocarcinomas, these differences will confound comparisons of survival rates between younger and older patients. Therefore the relative survival rate was also analysed separately for patients with a histopathologically proven adenocarcinoma. The exclusion of all tumours not reported as adenocarcinomas also included unspecified tumours (predominantly cases without a tumour biopsy). The proportion of unspecified tumours was higher in patients above the age of 40 years (*Table 2*). This difference must be kept in mind, since the group of unspecified tumours could contain a number of patients with adenocarcinomas at an advanced stage,

Table 6 *Number of cases and 5-year relative survival rate of patients reported to have a malignant tumour of the rectum and of cases with a histopathological diagnosis of adenocarcinoma. Figures presented by sex and age at diagnosis*

	Men				Women			
	All		Adenocarcinoma		All		Adenocarcinoma	
Age (years)	No.	5-year relative survivate rate	No.	5-year relative survival rate	No.	5-year relative survival rate	No.	5-year relative survival rate
0–9	1	100	0		0		0	
10–19	1	100	0		0		0	
20–29	38	37 6 (20·1–54·2)	31	28·7 (11 9–45·4)	29	49·7 (30 9–68·4)	21	46·6 (15 1–57 2)
30–39	135	48 3 (39·1–57 5)	122	44·3 (34·7–54 0)	42	50·4 (41·6–59 2)	126	45 8 (36 5–55 2)
<40	175	46·6 (38·6–54·6)	153	41·1 (32 6–49·5)	71	50·3 (42 3–58·3)	147	44·5 (36 0–53 1)
40–49	557	44·8 (40 4–49 3)	519	43·7 (39·1–48 4)	[illegible]45	54·6 (50·1–59·0)	485	52·5 (47·7–57 3)
50–59	2025	43 0 (40·5–45·4)	1916	43 6 (41 1–46·1)	1[illegible]36	51·3 (48 5–54·1)	1434	51 2 (48·4–54·1)
60–69	4187	43·3 (41·5–45·2)	3967	44·5 (42 6–46·4)	2[illegible]02	46 7 (44·5–48 8)	2610	47·6 (45 4–49·9)
70–79	4660	34·0 (32·0–36·0)	4293	36·2 (33·3–38·3)	3[illegible]96	41·9 (39 6–44·2)	2984	44 0 (41·6–46·5)
80+	2033	27 0 (23·3–42 2)	1664	31·0 (26 6–35·3)	1[illegible]16	26·6 (22·6–30 1)	1277	32·1 (27·4–36 9)
≥40	13462	39·1 (38·0–40 2)	12359	40 7 (39·6–41·9)	9795	44·7 (43 4–46 0)	8790	46·2 (44 9–47 6)

Values in parentheses are 95 per cent confidence intervals

not thoroughly investigated and with a bad prognosis. By excluding these patients from the survival analysis, the older patients with adenocarcinomas demonstrate a seemingly better prognosis.

Since the analysis of relative survival in patients with adenocarcinomas showed no differences in survival rates between the different age groups, it appears as if the better prognosis found in patients below the age of 40 years in the whole material is explained by a higher proportion of carcinoid tumours. This conclusion is further supported by the fact that the majority of all carcinoids was located in the right colon, where the survival differences were highest.

We conclude that patients below the age of 40 years with adenocarcinomas of the colon and rectum as a group have a prognosis which is similar to that in patients above that age. If all reported tumours of the colon and rectum are considered, patients below the age of 40 years show a better prognosis, which is probably because of the higher proportion of carcinoid tumours.

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Short note

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Response to faecal challenge in defunctioned colonic Crohn's disease: prediction of long-term course

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Split ileostomy is a useful procedure in the management of patients with Crohn's disease of the colon whose disease fails to respond to medical therapy or in whom local complications have developed[1–3] Harper *et al.*[4] found that patients with such a defunctioned colon frequently showed an adverse reaction to instilling ileostomy fluid into the isolated colon, suggesting that a constituent of the ileostomy effluent might be responsible for initiating inflammation. Ultrafiltration of the fluid did not have such an effect and they concluded that the responsible factor was greater than 22 nm in size. Recently, Winslet and Keighley[5] have reported similar results. Hence the response to faecal challenge in patients with a defunctioned colon might be used to predict the subsequent course of the disease following restoration of intestinal continuity. The purpose of this study was to describe the subsequent clinical course of the patients studied by Harper *et al.* and relate this course to the patient's response in the challenge studies.

Patients

Of the 15 patients who were originally challenged with their ileostomy fluid[4], nine (mean age 40·5 years, range 25–71 years) were subsequently reconnected. Six (mean age 43 6 years, range 37–49 years) were not rejoined All the patients have been under regular follow-up (*Table 1*).

Results

Six patients received a split ileostomy for Crohn's colitis and were not subsequently rejoined; one of these (No. 15) felt so well that he refused reconnection and he has remained well. He had had no response to faecal challenge. Four patients (Nos 11–14) had had a positive challenge and their disease did not settle sufficiently to allow intestinal continuity to be restored; they all came to colectomy. The median time from challenge to colectomy was 1·5 months (range 0–22 months) The sixth patient (No. 10) had had a negative challenge and was well for many months but was not joined up because of perianal disease which, although initially controlled, required excisional surgery after 78 months.

Table 1 *Patient details*

Patient no	Sex	Age* (years)	Months defunctioned	Months between challenge and rejoining	Subsequent follow-up (months)	Extent of disease at challenge
Subsequently rejoined						
1	M	31	21	1	46	Whole colon
2	F	71	11	65	5	Rectum (previous IRA)
3	F	25	10	5	50	Rectum + transverse + sigmoid
4	M	39	6	6	75	Right colon + transverse + rectum
5	M	33	8	2	66	Right colon + transverse + descending
6	M	41	21	1	90	Ileum + whole colon
7	M	54	21	28	48	Sigmoid + rectum (previous left hemicolectomy)
8	F	33	27	15	55	Whole colon + perineum
9	F	37	29	50	45	Rectum + sigmoid (previous IRA + ileal resection)
Patients not rejoined						
10	M	44	22	–	78	Rectum (previous IRA) + perineum
11	F	49	25	–	36	Whole colon
12	F	37	12	–	69	Rectum (previous IRA)
13	F	45	13	–	24	Ascending + part of transverse + sigmoid + rectum
14	F	48	36	–	73	Whole colon
15	M	39	24	–	76	Whole colon

* At end of follow-up IRA, ileorectal anastomosis

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Table 2 *Long-term clinical course in relation to the response to faecal challenge in the reconnected patients*

	Response to challenge	Subsequent course (months after rejoining)
Negative challenge (patient no.)		
1	–	Ileocaecal resection (28)
2	–	Proctectomy (3)
3	–	Ileocaecal resection (8) then four relapses
4	–	Subtotal colectomy + resection of terminal ileum (7)
5	–	Seven relapses followed by excisional surgery (64)
6	–	Well
Positive challenge (patient no.)		
7	Aphthoid mouth ulcers	Well
8	Severe abdominal pain + flare-up of perianal disease	Well
9	Mucus discharge per rectum	Eight relapses

Of the nine patients who were rejoined, three remained well and required no further surgery during follow-up (48, 55 and 90 months) Two of these patients had had a positive challenge. The other six who were rejoined had an unfavourable course and all required excisional surgery at a median time of 8 months (range 3–64 months) following reconnection. Five of these six patients had had a negative response to challenge.

Table 2 correlates the initial result of the faecal challenge with the subsequent clinical course in the nine patients in whom intestinal continuity was restored. Of the six patients with a negative response to challenge, only one did well (No 6) whereas two (Nos 2 and 7) of the three with a positive response have done well. Thus, response to faecal challenge failed to predict subsequent outcome

Discussion

The immediate value of faecal diversion in the management of Crohn's disease of the colon has been documented in several centres[1,2,6,7] although favourable results have not always been achieved[8] Most controversy exists over the subsequent course of the disease. Many centres have been able to restore continuity in less than one-third of patients and even then there has been a rapid relapse[7,9–12]. Others have reported much more encouraging results with continuity being restored in about two-thirds with many patients then having a favourable course[1,2,6]

Could the results of a faecal challenge predict those patients who would do well following anatomical restoration? This was suggested by Kivel *et al.*[13], and Winslet and Keighley[5] only closed the split ileostomy in patients having a negative challenge

Long-term follow-up of the Oxford series[4] shows that the response to a challenge correlates poorly with the subsequent clinical course. The numbers of patients available for study are small but, even so, there is little to suggest that the results of such challenges would have been useful in deciding future management. Nevertheless, the negative results originally obtained using an ultrafiltrate in contrast to the crude effluent[4], together with the response of active Crohn's disease to an elemental diet[14], provide some evidence that constituents of ileal or colonic contents have a role in the inflammatory response. More precise characterization of these constituents might lead not only to better understanding of the pathogenesis but also to a more precise and meaningful challenge test.

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High *versus* low ligation of the inferior mesenteric artery in rectal cancer

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The argument for and against high ligation of the inferior mesenteric artery in rectal cancer has yet to be resolved. Between 1948 and 1983, 4250 patients underwent surgery for rectal carcinoma at St. Mark's Hospital, London. From these, 250 patients were selected who had undergone curative anterior resection of a Dukes' C adenocarcinoma and their records were examined. In 150 (60 per cent) the inferior mesenteric artery was ligated above the origin of the left colic artery. The outcome was analysed using the Dukes', Gastrointestinal Tumour Study Group and Astler–Coller classifications, either alone or in combination. Tumour differentiation and extent of local invasion were also considered. Despite this detailed analysis, no improved survival was seen in patients when the inferior mesenteric artery was ligated above the origin of the left colic artery.

Keywords: Rectal neoplasm, surgery, mortality

Should the inferior mesenteric artery be divided flush with the aorta or at the pelvic brim when operating on a patient with rectal cancer? High ligation allows more radical excision of the lymphatic drainage which increases the chance of removing all involved lymph nodes and should improve prognosis[1,2]. It can jeopardize the blood supply to the proximal side of an anastomosis, however, and may occasionally result in the need for more extensive surgery.

In past reports some patients with histologically proven involvement of the apical lymph node (Dukes' C2) live for a long time[3–5]. In the Large Bowel Cancer Project[6] approximately 20 per cent of patients with Dukes' C2 lived for 5 years. The involved apical lymph node was the last site of involvement in such patients or the balance, in immunological terms, was tilted sufficiently in favour of host defence mechanisms for a cure to be achieved

Studies by Rosi *et al.*[7], Grinnell[8] and Pezim and Nicholls[9] have not shown any advantage in performing a high ligation. In the last paper from St. Mark's Hospital[9] the authors considered all curative operations for rectal tumours, both restorative and excisional and of all Dukes' stages. Dukes' C1 tumours were subdivided according to the number of lymph nodes involved (four or less and five or more) but no difference could be shown between those having high or low ligation. The level of ligation may have no effect on the survival of patients with Dukes' A and B tumours without lymph node involvement and should have greatest effect on Dukes' C2 tumours rather than Dukes' C1.

This report uses a highly selected group of patients and applies several different criteria, alone and in combination, to study this phenomenon.

Patients and methods

Between 1948 and 1983, 4250 patients underwent surgery for rectal cancer at St. Mark's Hospital Of these, 250 patients were selected who had undergone a curative anterior resection for a Dukes' C tumour. Patients who had a palliative operation or who died within 28 days of surgery were excluded as were those with multiple tumours, previous ulcerative colitis or proven earlier malignancy at any site. Three patients were excluded as the level of ligation of the inferior mesenteric artery could not be assessed accurately from the records

Patients were divided into those having a high or low ligation and a number of variables were examined, particularly those relating to nodal involvement. In patients having a high ligation more lymph nodes are removed. This could affect the distribution of Dukes' C1 and C2 tumours, possibly making direct comparison of high and low ligation inaccurate. Other classifications of C status are likely to be less affected by the level of vascular tie Survival has been evaluated using the original Dukes' classification[10], the Gastrointestinal Tumour Study Group's criteria and the Astler–Coller modifications The Gastrointestinal Tumour Study Group's modification[11] depends on the number of involved lymph nodes; C1 tumours are those with four or fewer nodes affected while C2 tumours have five or more. The Astler–Coller modification[12] depends on the depth of primary tumour penetration in the presence of involved nodes, C1 tumours are those limited to the bowel wall and C2 are those with extrarectal spread.

The prognosis in a patient with a Dukes' C2 tumour treated by low ligation might have been improved if a high ligation had resulted in conversion to a C1 status. To elucidate this point we have selected a 'standard lymph node' (the 12th node from the tumour) as it was shown that the mean number of nodes examined in the low ligation patients was 11·9. A group of patients undergoing high ligation and with this node involved (irrespective of whether the apical node was actually involved) was isolated and their survival was compared with that of patients with apical lymph node involvement (Dukes' C2) treated by low ligation to see if there was any advantage.

Results

Of the 250 patients selected, 132 (53 per cent) were men and 150 (60 per cent) were treated by high vascular ligation There was an even sex distribution between high and low ligation groups, but the average age in the former group was 56 years (range 24–80 years) compared with 64 years (range 34–87 years) in the latter group (not significant). Five-year follow-up was achieved in 244 (98 per cent) patients.

Pathological variables (Table 1)

Tumour height. The level of the tumour from the anal verge was assessed before operation by sigmoidoscopy. More tumours were situated in the lower and middle rectum in the high ligation group ($\chi^2 = 7\cdot93$, $P < 0\cdot01$).

Tumour differentiation. There was no difference in distribution of tumour grade between the high and low ligation groups.

Local invasion The extent of local invasion was similar in the two groups.

Lymph nodes. The mean number of lymph nodes examined in the high ligation group was 14·2 and in the low group was 11·9.

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Table 1 *Pathological variables: all cases*

	High ligation ($n=150$)	Low ligation ($n=100$)
Level of tumour		
Lower rectum	3 (2)	–
Middle rectum	29 (19)	8 (8)
Upper rectum	80 (53)	72 (72)
Rectosigmoid	38 (25)	20 (20)
Tumour differentiation		
Well	16 (11)	15 (15)
Moderate	102 (68)	73 (73)
Poor	33 (22)	12 (12)
Local invasion		
Nil	13 (9)	14 (14)
0–4 mm	58 (39)	40 (40)
5–9 mm	41 (27)	24 (24)
≥10 mm	38 (25)	22 (22)
Lymph nodes examined		
Range	4–38	2–26
Median	17	13
Mean	14·2	11·9

Values in parentheses are percentages

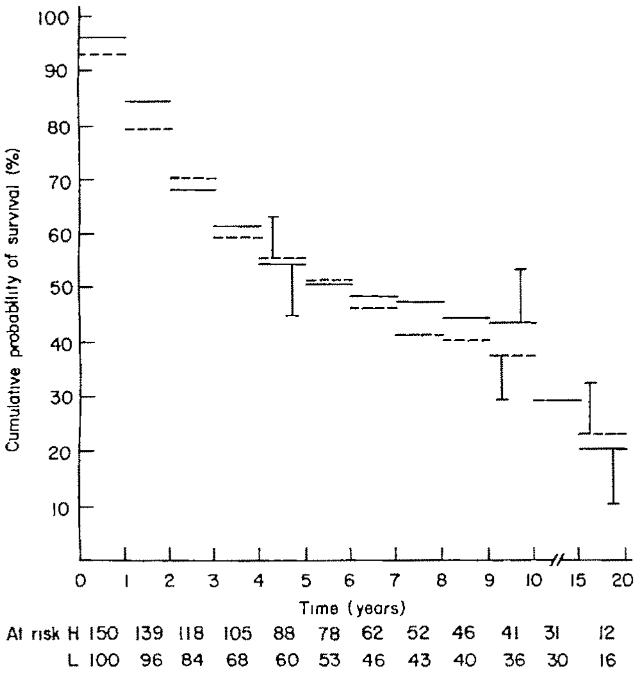

Figure 1 *Comparison of cumulative probability of survival in all cases Error bars represent 95 per cent confidence limits* L, *low ligation* (——); H, *high ligation* (----)

Overall survival rates

The survival rates in the high and low ligation groups were compared actuarially (*Figure 1*). There was no significant difference between the two groups.

Survival rates in the Astler–Coller classification

Two hundred and twenty-three (89 per cent) were Astler–Coller C2 tumours. There was no difference in the distribution of C1 and C2 tumours between the two groups to suggest that high ligation was being reserved for inherently less favourable tumours. Survival rates were similar in the high and low ligation groups, respectively 77 *versus* 80 per cent at 5 years and 67 *versus* 72 per cent at 10 years in C1 tumours, while in C2 tumours the results were 53 *versus* 51 per cent at 5 years and 33 *versus* 39 per cent at 10 years

Survival rates in the Gastrointestinal Tumour Study Group's classification

One hundred and ninety-five (78 per cent) were C1 tumours, evenly distributed between high and low ligation. Analysis revealed similar survival rates for C1 (64 *versus* 56 per cent at 5 years and 45 *versus* 44 per cent at 10 years) and C2 tumours (34 *versus* 20 per cent at 5 years and 23 *versus* 12 per cent at 10 years) in the high and low vascular ligation groups respectively.

Survival rates in the Dukes' classification

Of the 250 cases, 207 (83 per cent) were Dukes' C1, with an even distribution between high and low ligation. Survival rates in Dukes' C1 tumours showed no significant difference between the two groups: 64 *versus* 54 per cent at 5 years and 44 *versus* 42 per cent at 10 years in the high and low ligation patients respectively.

Examination of the Dukes' C2 tumours showed an apparently improved survival rate in patients treated by low ligation (*Figure 2*). There was no difference in the incidence of Astler–Coller C1 and C2 tumours, Gastrointestinal Tumour

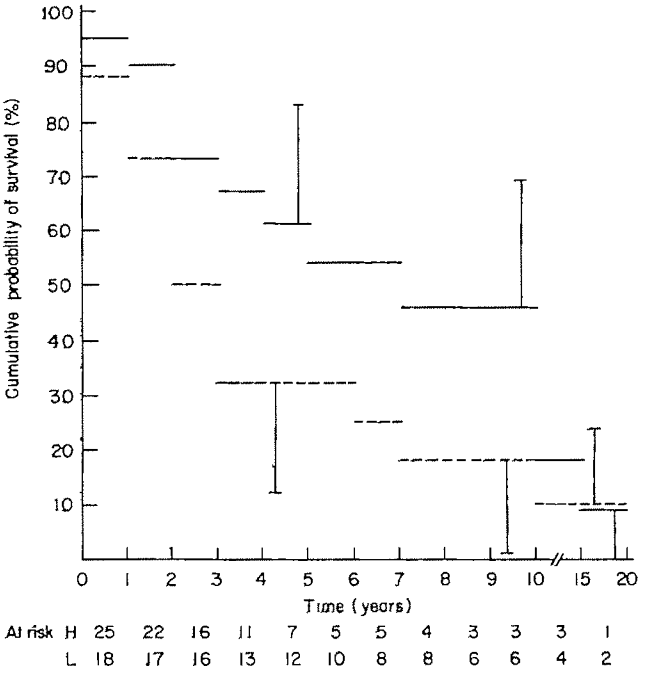

Figure 2 *Comparison of cumulative probability of survival in Dukes' C2 tumours. Error bars represent 95 per cent confidence limits* L, *low ligation* (——), H, *high ligation* (----)

Table 2 *Pathological variables in Dukes' C2 tumours*

	High ligation ($n=25$)	Low ligation ($n=18$)	P
Astler–Coller classification			
C1	0	1 (6)	
C2	25 (100)	17 (94)	
Gastrointestinal Tumour Study Group classification			
C1	12 (48)	11 (61)	
C2	13 (52)	7 (39)	<0·5*
Tumour differentiation			
Moderate	17 (68)	15 (83)	
Poor	8 (32)	3 (17)	0·15†
Tumour invasion			
<5 mm	4 (16)	9 (50)	
≥5 mm	21 (84)	9 (50)	0·016†

Values in parentheses are percentages; * χ^2 test; † Fisher's exact test

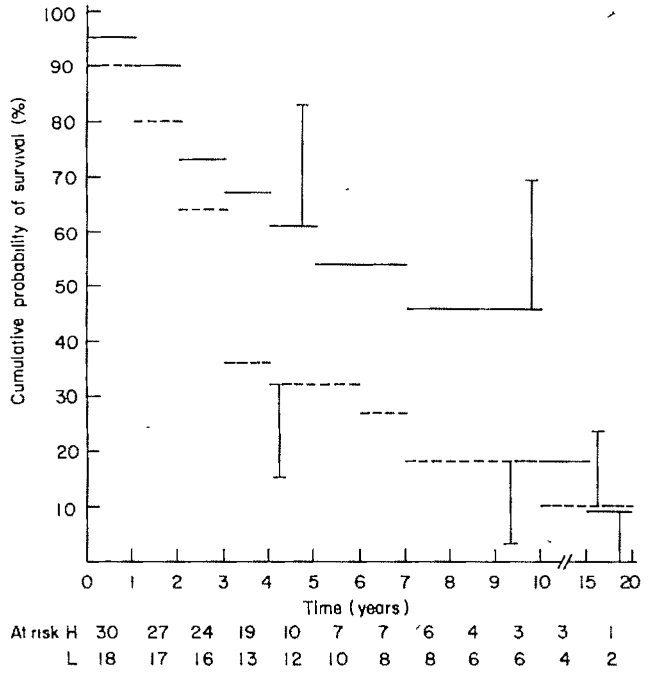

Figure 3 *Comparison of cumulative probability of survival in standard lymph node C2 tumours treated by high ligation and Dukes' C2 tumours treated by low ligation. Error bars represent 95 per cent confidence limits* L, *low ligation* (----); H, *high ligation* (——)

Study Group C1 and C2 tumours or in the degree of tumour differentiation between high and low ligation patients. Analysis of the extent of tumour invasion revealed more patients with extrarectal invasion $\geqslant 5$ mm (poorer prognosis) in the high ligation group (21 of 25 (84 per cent) *versus* nine of 18 (50 per cent); $P=0{\cdot}016$, Fisher's exact test) (*Table 2*).

Standard (12th) lymph node involvement

One hundred and forty-one patients had at least 12 lymph nodes examined and a copy of the pathological chart available for study. Of these, 78 (55 per cent) were men and 96 (68 per cent) underwent high vascular ligation. Twenty-two patients in the high group had involvement of the 12th or standard lymph node.

A comparison of survival rates between these patients and those with a Dukes' C2 tumour treated by low ligation was then made. This showed an apparent improvement in survival in low ligation patients but this failed to reach statistical significance (*Figure 3*). Further assessment revealed an equal incidence of Astler–Coller and Gastrointestinal Tumour Study Group C1 and C2 tumours, as well as equal depth of tumour invasion in the two groups. There were significantly more poorly differentiated tumours in the high ligation or standard lymph node group (22 of 30 (73 per cent) *versus* three of 18 (17 per cent); $\chi^2=14{\cdot}47$, $P<0{\cdot}001$).

Discussion

The possible improvement in prognosis from high ligation must be balanced against the risks of more extensive surgery being required. The marginal artery may be of poor quality in the region of the descending colon between the final two divisions of the left colic artery[13] and care must be taken to preserve these two final branches as a support to the marginal artery in this area.

The average age of patients was lower in the high ligation group (56 *versus* 64 years) but this was not statistically significant. One possible reason for this difference could be a desire by the surgeon to do the maximum possible in attempting to cure a younger patient by performing a high ligation.

Analysis of the level of the tumour from the anal verge, the degree of tumour differentiation and local invasion revealed no obvious difference between high and low ligation groups. There were more tumours in the lower and middle rectum in the high ligation group, probably because of technical reasons. When performing a very low anastomosis sufficient length of proximal bowel must be obtained to allow the anastomosis in the pelvis without tension. This degree of mobilization usually requires division of the inferior mesenteric artery proximal to the left colic artery, relying on the middle colic and marginal arteries for blood supply.

Analysis of survival rates using life-tables in all cases, Astler–Coller C1 and C2 cases, Gastrointestinal Tumour Study Group C1 and C2 cases and Dukes' C1 tumours, revealed no significant advantage with high ligation. Examination of the Dukes' C2 tumours at 5 and 10 years failed to reach statistical significance. Further examination revealed an unequal distribution of the extent of tumour invasion in favour of the low ligation group. This may explain the apparent advantage but the numbers were too small to allow full assessment of the impact of this difference

Comparison of the isolated group with the standard (12th) lymph node involved treated by high ligation and Dukes' C2 cases treated by low ligation revealed no statistically significant improvement in prognosis in the latter group. Further assessment showed an excess of poorly differentiated tumours in the high ligation or standard lymph node group and this may reflect defects in the method used.

Several studies in the past[7,8,14] have attempted to show improved survival with high vascular ligation. The most recent study by Pezim and Nicholls[9] subdivided Dukes' C1 tumours by the number of lymph nodes involved but did not show any advantage in high ligation. The question has been re-examined with particular reference to Dukes' C2 tumours. This has not shown any advantage with high vascular ligation. The present study, possibly the largest with complete records that can be achieved from one hospital, has failed to isolate any group of patients with Dukes' C rectal carcinoma that has benefited from high vascular ligation The question may be resolved only by including this surgical aspect in one of the current multicentre trials when larger numbers may enable small differences to become apparent.

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Short note

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Restorative proctocolectomy without temporary ileostomy

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When performing restorative proctocolectomy it has been accepted practice to defunction the reservoir with a temporary proximal loop ileostomy. The presence of an ileostomy and its subsequent closure may result in complications. We have attempted to reduce the number of operative procedures and the total hospital in-patient stay by omitting the defunctioning ileostomy in carefully selected cases. The results are presented and an assessment is made to determine whether such a policy is justified.

Patients and methods

Between January 1984 and March 1989, 64 patients underwent restorative proctocolectomy with W reservoir. The technique employed hand-suturing of both the reservoir and the ileoanal anastomosis[1] In 35 patients a temporary ileostomy was performed to defunction the pouch, in 29 this was omitted The decision whether or not to perform a temporary ileostomy was taken after completion of the ileoanal anastomosis. No absolute criteria were used in making this decision but the ease of construction of the reservoir and in particular the ileoanal anastomosis, the presence and degree of any contamination, the tension on the ileoanal anastomosis and the dose of steroids were taken into account If conditions were considered optimal, the ileostomy was omitted.

There was no significant difference in age between the two groups. The ileoanal anastomosis was found to be more difficult in men, particularly if they had large muscular buttocks, and 61 per cent required ileostomy compared with 46 per cent of women. Forty-two per cent of patients with familial adenomatous polyposis had a stoma compared with 58 per cent of patients with inflammatory bowel disease, while 34 per cent of patients receiving prednisolone in a dose exceeding 10 mg daily had a stoma, compared with only 10 per cent of those receiving no steroids or a dose of less than 10 mg daily.

The first ten patients in the series all had defunctioning ileostomies It was only with increased experience of the operation that it was omitted

Results

Details of complications are given in *Table 1*; there were no deaths in either group. The morbidity resulting from these complications and the mean hospital in-patient stay are given in *Table 2*.

Discussion

It is now more than 40 years since Ravitch introduced the concept of total colectomy, mucosal proctectomy and ileoanal anastomosis for the treatment of diseases confined to the large bowel mucosa[2]. High complication rates and poor functional results engendered little enthusiasm for this procedure until the late 1970s when Parks and Nicholls from St. Mark's Hospital in London, UK, described the addition of a small bowel reservoir and reported good functional results[3]

Although refinements have been made to the construction of the pouch, it has always been accepted practice to perform a temporary defunctioning loop ileostomy. In one large series of 369 restorative proctocolectomies from the Mayo clinic[4], all cases had a temporary ileostomy and the authors stated that 'failure to divert the faecal stream invites disaster', an opinion shared by others[5], although they themselves reported obstruction, sepsis, retraction and high output as complications of the stoma or its closure.

In a series of W pouches from St. Mark's Hospital[6], identical in size to this series, all patients received an ileostomy. The authors report a total of 32 complications in the 64 patients, with a 25 per cent sepsis rate (wound infection, pelvic sepsis

Table 1 *Postoperative complications*

	Stoma (*n* = 35)		No stoma (*n* = 29)
	Related to pouch operation	Related to ileostomy	
Sepsis			
Peritoneal	3(1)		1
Pelvic	1		
Wound	1		1
Anastomotic leak			
Pouch			2(1)
Ileoanal anastomosis			2(1)
Ileostomy closure		2(2)	
Obstruction	3	2(1)	2(1)
Toxic psychosis	1		
Retraction of stoma		1(1)	
Deep venous thrombosis			1
Total	14(5)		9(3)

Values in parentheses are the number of cases requiring further surgery

Table 2 *Overall outcome*

	Stoma (*n* = 35)	No stoma (*n* = 29)
No. of patients with complications (%)	11(31)	9(31)
Total no. of complications	14	9
Complications requiring surgery (%)	5(14)	3(10)
Total no of operations	75	33
Mean no of days in hospital (range)	25 3(13–121)	17 3(8–101)

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and anastomotic leakage combined), and 13 per cent of patients required laparotomy for obstruction. Their average total in-patient stay was 24 days. The complications in our 35 patients with an ileostomy compare favourably with these, and have a similar average duration of hospitalization indicating that we are not comparing our stoma-free patients with a particularly poor-risk group.

We would not advocate omitting the ileostomy until a surgeon has gained reasonable proficiency with the operation and the importance of experience, particularly in performing the ileoanal anastomosis, cannot be understated. It is recommended that in general an ileostomy should be performed in patients receiving high doses of steroids because of impaired healing, which explains the greater proportion of stomas in patients with inflammatory bowel disease compared with familial adenomatous polyposis.

The higher incidence of anastomotic leakage in patients with no ileostomy is cause for concern. In several cases the dehiscence appeared to occur about the time when the catheter draining the pouch was removed or fell out. We believe that to drain the reservoir is almost as effective as defunctioning it with an ileostomy and now make a point of leaving the catheter in for 7 days, by which time the strength of the suture line is increasing.

It has been suggested that following restorative proctocolectomy there may be transient incontinence due to stretching of the anorectal sphincters while performing the ileoanal anastomosis, and that an ileostomy is required while this settles down. This has not been our experience.

This study demonstrates that the benefit in terms of reducing the number of operative procedures and hospital stay can be considerable if an ileostomy is avoided, and this is not at the expense of an increased morbidity rate. Indeed the overall complication rate is less and the mean duration of hospital stay is reduced. In addition it is clear that the presence of a stoma and its subsequent closure are themselves associated with an appreciable morbidity, making it positively advantageous to avoid a stoma in suitable cases.

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Association between transfusion with plasma and the recurrence of colorectal carcinoma

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Data was collected from patients with colonic or rectal tumours undergoing potentially curative surgery. Univariate analysis showed an association between perioperative transfusion with plasma and the earlier recurrence of tumour. Allowing for possible confounding factors the relative risk of recurrence for patients receiving plasma was 2·44 (95 per cent confidence interval = 1·10–5·46, P = 0·041) and for patients receiving whole blood or plasma, it was 2·39 (95 per cent confidence interval = 1·19–4·83, P = 0·021). The risk of recurrence for those receiving a transfusion of plasma was, therefore, more than twice that of those not given it. We were unable to demonstrate an independent harmful effect of transfusion with packed cells. These data suggest that the plasma protein, rather than the cellular component of whole blood, mediates the accelerated tumour recurrence.

Keywords: Blood transfusion, colonic neoplasm

Since the report by Burrows and Tartter[1] there has been much debate over whether perioperative blood transfusion during surgery for malignancy may have an adverse effect on tumour recurrence. There have been numerous retrospective studies demonstrating an adverse effect for colorectal carcinoma[2–7] and cancers of the breast[8], cervix[9], lung[10] and stomach[11]. Blumberg *et al.* have shown that whole blood is more harmful in this respect than packed cells, and in that more than three units of packed cells but only one unit of whole blood are required to detect a harmful effect[12,13].

Several studies have failed to demonstrate a statistically significant harmful effect for colorectal[14–17], breast[5], renal[18] and lung[19] tumours.

This study examines the experience in this centre and whether transfusion with different products carries different risks.

Patients and methods

Two hundred and twenty-four patients (1980–84) with Dukes' B or C carcinoma of the colon or rectum, with specimen resection margins free of tumour, were identified from pathology reports. Of these, 31 case notes could not be traced. A further 36 were found to have had macroscopic evidence of dissemination of the tumour beyond the resection margins, either locally, transperitoneally or to the liver. We excluded nine who died within 2 weeks of operation on the grounds that it was impossible to know whether tumour had recurred or not. We also excluded four with ulcerative colitis, two with polyposis coli, one with Gardner's syndrome, two with synchronous primaries, five with other malignant tumours and two for whom anaesthetic or operation records were not available. This left 132 patients who had undergone potentially curative surgery for Dukes' B or C disease.

From the records of these cases, details were abstracted for the main prognostic variables known to affect tumour recurrence. These were: the patient's age, whether the operation was an emergency (i.e. whether performed on obstructed bowel), tumour site and the pathological stage. We also recorded as variables for inclusion in the proportional hazards analysis the patient's sex, the operation starting time and duration, the seniority of the surgeon, the blood loss (if recorded), the immediately preoperative and the first postoperative haemoglobin level. For patients who had an initial defunctioning colostomy the definitive operation was not regarded as emergency. For whole blood, packed cells and plasma given during the period 30 days either side of the operation we noted the amount given and the time relative to the start of the operation. The term plasma included those receiving fresh frozen plasma ($n = 1$) and those receiving fractionated and pasteurized plasma protein solution ($n = 13$).

The duration of recurrence-free survival following operation was obtained from records of hospital follow-up. Recurrence was manifest by the finding of tumour at biopsy or a second operation, liver metastases at ultrasound or clinical carcinomatosis. The general practitioner was contacted for further information on any case for whom hospital records did not provide a definite endpoint. As a final check, all cases of uncertain outcome were checked against a listing of death certifications with any mention of colonic or rectal carcinoma obtained from the Registrar General for Scotland. The endpoints of the study were thus. (1) the earliest known recurrence of tumour after surgery (in two cases the earliest known recurrence was the date of death certification); (2) tumour-free survival to the end of the study period, and (3) loss of contact with both the hospital and general practitioner (11 patients) but not registered as a death due to tumour within the region. These latter patients were treated as censored at the time of last contact for the analysis.

Statistical methods

We were interested in the separate effects of red cells and plasma on tumour recurrence. Some patients were transfused with both packed cells and plasma and of course some received whole blood which contains both these constituents. In order to try and separate the effects the patients were initially divided into groups defined by three separate transfusion variables (1, 2 and 3) according to the constituents of the transfusion fluids they had received:

1. Whether the patient received any transfusion fluid at all ($n = 62$) or not ($n = 70$).
2. Whether the patient received any fluid containing red blood cells (i.e. packed cells and/or whole blood, $n = 57$) or not ($n = 57$).
3. Whether the patient received any fluid containing significant plasma (i.e. whole blood and/or plasma protein fraction, $n = 23$) or not ($n = 109$).

The numbers of patients in these groups and the overlap between the groups are shown in *Figure 1*.

To compare the characteristics of the patient groups for variables known to affect the prognosis for tumour recurrence, χ^2 tests for categorical data and unpaired t tests were used. These variables were age, tumour site, tumour stage and whether or not the operation was an emergency.

Univariate Mantel–Cox tests were used to assess the difference in time to tumour recurrence, defined by the transfusion variable groups. Multivariate analysis using the proportional hazards regression model of Cox[20] was used to assess the effect of all variables on the time to recurrence of tumour. This approach estimates the effect of a given variable whilst allowing for possible confounding by other variables. All analyses were carried out using the statistical software package, BMDP (BMDP Statistical Software, Los Angeles, California, USA)[21].

Analysis by application of these methods to the transfusion variables (1, 2 and 3) listed above suggested a harmful effect of plasma. We

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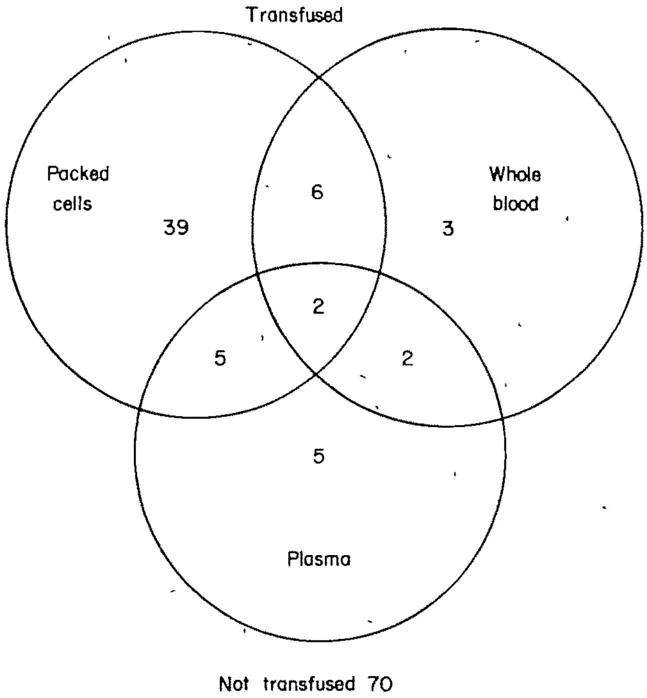

Figure 1 *Numbers of patients who received each transfusion product*

Table 1 *Univariate analysis of the effect of transfusion variables on the time to tumour recurrence*

Transfusion variable	*n*	Mean survival (years)	χ^2 (1 degree of freedom)	*P* value
1 Received:				
Any transfusion	62	5·3	1·39	0·24
No transfusion	70	6·14		
2 Received:				
Any product containing red cells	57	5·28	1·27	0·26
No product containing red cells	75	6·08		
3 Received:				
Whole blood or plasma	23	3·96	4·95	0·026
No whole blood or plasma	109	6·05		

therefore subsequently applied the same statistical methods to different patient groupings (see below)

Results

The univariate analysis (*Table 1*) revealed that the only transfusion variable which had a significant effect on time to tumour recurrence was '3', i.e. whether or not the patient was transfused with whole blood and/or plasma ($P = 0{\cdot}026$). *Figure 2* shows the time to tumour recurrence curves for this patient grouping.

Table 2 shows the comparison, in terms of known prognostic indicators, of the patients when grouped by transfusion variable '3', together with recurrence rates for these groups. Note that although patients in the transfused group were younger, that it had a smaller proportion of Dukes' C tumours, a greater proportion of rectal tumours and a greater proportion of emergency surgery, none of these differences were statistically significant and all were allowed for in the multivariate analysis.

The proportional hazards model was fitted with all the variables for each of the three transfusion variables separately. Dukes' C carcinoma was associated with a relative risk of 1·45 of recurrence compared with Dukes' B. This result did not attain statistical significance, the 95 per cent confidence interval being 0·80–2·64. Age was significantly associated ($P = 0{\cdot}007$) with time to recurrence for all three analyses. The regression coefficient for age was 0·05 (95 per cent confidence interval = 0·017–0·083, fitted with transfusion variable '3' in the model). This means older patients had a shorter time to recurrence with a relative risk of 1·05 for each year of age. The only other variable significantly and independently associated with time to tumour recurrence was transfusion variable '3'. The relative risk of recurrence for patients who received any whole blood or plasma was 2·39 (95 per cent confidence interval = 1·19–4·83, $P = 0{\cdot}021$).

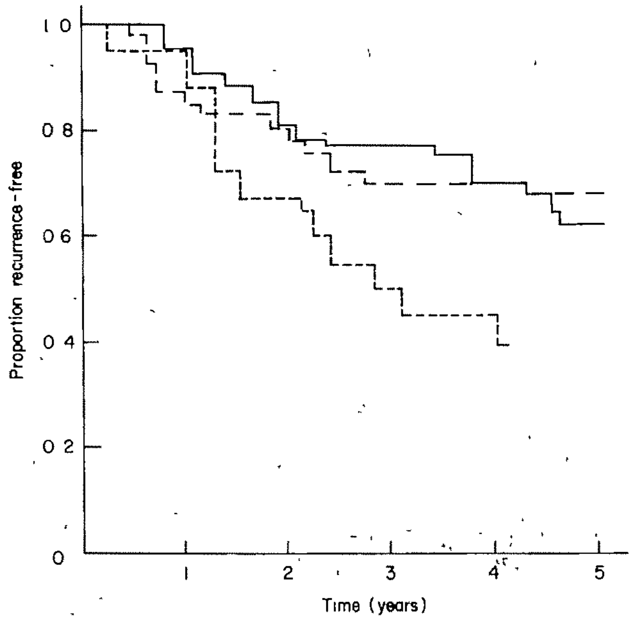

Figure 2 *Time from surgery to recurrence of tumour. The patients are grouped by the products transfused perioperatively.* – – · –, *Packed cells only;* – – –, *whole blood or plasma (whether or not packed cells were given as well),* ——, *no transfusion. The recurrence-free curve for the whole blood or plasma group differs statistically from the other two curves combined (log rank test,* P = *0·026)*

Table 2 *Comparison of the characteristics of the patients grouped according to transfusion variable '3'*

	Not transfused with whole blood or plasma		Transfused with whole blood or plasma
Mean age	69·3		67·4
Number of patients	109	(n.s.)	23
Site			
Colon	76		12
Rectum	33		11
Total	109	(n.s.)	23
Classification			
Dukes' B	59		14
Dukes' C	50		9
Total	109	(n.s.)	23
Non-emergency	94		18
Emergency	15		5
Total	109	(n.s.)	23
No recurrence	74		10
Recurrence	35		13
Total	109	$P = 0{\cdot}0049$	23

n.s., Not significant

The relative risk of recurrence for patients who received red cells only ($n=39$) compared with no transfusion was not significant (0·98, 95 per cent confidence interval=0·47–2·03, $P=0{\cdot}84$).

We therefore analysed the data for the separate effects of receiving whole blood (13 patients) and plasma (14 patients, see *Figure 1*). Transfusion with plasma, irrespective of other products, was significantly harmful ($P=0{\cdot}041$, relative risk=2·44, 95 per cent confidence interval=1·10–5·46). Transfusion with whole blood had a relative risk of 2·47 (95 per cent confidence interval=0·98–6·25) but did not reach statistical significance ($P=0{\cdot}073$) unless the variable was combined with plasma (see above).

Finally, we repeated all the above analyses, but further subdividing the transfusion groups according to the timing of their transfusion relative to the operation. We could find no significant difference between those receiving transfusions before, during or after surgery.

Discussion

The salient positive finding is that the perioperative transfusion with plasma is associated with an approximate doubling of likelihood of tumour recurrence. Our results also agree with the findings of Blumberg and colleagues[12,13] of an association between receiving whole blood and tumour recurrence, although whole blood alone did not reach statistical significance in our study. Our data set is smaller and confined to tumours in one organ. We have not been able to confirm the previously reported harmful association for recipients of packed cells alone Our results suggest that the harmful effect seen with whole blood is also seen with plasma alone, suggesting that the plasma protein rather than the leucocyte component is the important mediator. This is in keeping with the knowledge that there are few viable leucocytes in normally stored whole blood. We have not attempted to distinguish between the individual patient who received fresh frozen plasma and the 13 who received stable plasma protein solution. These two products do differ in many ways, particularly the content of larger protein molecules (fibrinogen and immunoglobulins) is largely degraded by the pasteurization of the stable preparation.

Apart from the effect of transfusion, the only other variable significantly associated with tumour recurrence was the patient's age. Dukes' classification, widely accepted as being of prognostic importance, did not attain statistical significance. The explanation may be that we deliberately collected data on only two Dukes' classifications (2 and 3) unlike other authors[12]. We excluded Dukes' A and Dukes' D since we felt that their uniformly good and poor prognosis respectively would yield little information about other factors affecting prognosis. A further explanation of the lack of statistically significant effect of Dukes' classification may lie in our relatively small number of patients.

There are two main implications from this type of study. First, if the association between receiving plasma protein and tumour recurrence is a causal one, we need to identify (and perhaps remove) those components of plasma that have this effect. There is evidence in mice[22] that plasma transfusion increases tumour growth but other work[23] in rats implicates the erythrocyte and leucocyte components as the important mediators.

Second, there are practical implications for patients undergoing this type of surgery It is already reasonably accepted that transfusion should only be given if clinically important. We confirm the recommendation that if transfusion is necessary, packed cells should be used in preference to whole blood and further that the packed cells combined with plasma protein fraction does not avoid the risk of giving whole blood. There is evidence from animal work that autologous transfusion is not harmful[24] but this would not be practical for the majority of these patients. Artificial blood remains a theoretical possibility. There may be serious ethical problems with a controlled trial of transfusion with packed cells *versus* whole blood in that this would be testing a treatment that is thought to be potentially harmful rather than beneficial. A trial of 'washed' red cells (which contain even less plasma than packed cells) may help to identify if the harmful effect is confined to the plasma fraction. Large numbers of patients would be needed since it is only the larger studies which have demonstrated a harmful effect of receiving packed cells[13] and then only if given in large amounts. Other authors might analyse their data to see if they can confirm an independent harmful effect of plasma protein fraction.

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Short note

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Wound infection after abdominal incision with scalpel or diathermy

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There is no controlled clinical study of wound healing after different techniques of abdominal incision. The scalpel produces a clean, incised wound with minimal tissue destruction. Diathermy produces a burn of variable depth in the tissue, but may reduce bleeding and make the incision quicker.

A study in the rat[1] confirmed that diathermy results in slower healing of the skin than scalpel incision, but there was no difference in wound bursting strengths. There was more infection after diathermy incision than after scalpel incision[2].

In this study, we randomized patients to have the abdominal incision made by knife or diathermy, and we prospectively recorded the time required to make the incision and the wound infection rate.

Patients and methods

A total of 240 consecutive patients were randomly allocated to have the abdominal incision made either with a surgical scalpel or with cutting diathermy. Midline incisions were made using the allocated technique through all layers. Muscle cutting incisions were made using the allocated technique for the subcutaneous fat and deep fascia only; the muscle was cut using diathermy.

Patients undergoing reoperation within 1 month of laparotomy and patients with ruptured abdominal aortic aneurysm were excluded.

Wounds were classified according to the site and direction of the wound, the presence of a previous incision and the degree of operative contamination[3]. The length of the wound and depth of subcutaneous fat were recorded The time was recorded from the start of the skin incision to completion of the peritoneal incision with complete haemostasis. A uniform policy of prophylactic antibiotic cover was used and established infection was treated as appropriate. Peritoneal lavage was performed with chlorhexidine in normal saline in cases with peritoneal contamination or infection. All incisions were closed using a mass suture technique. Subcutaneous sutures and subcutaneous drains were not used.

Wounds were inspected daily. Any sign of sepsis was recorded. Wound infection was defined as the discharge of pus or fluid containing pathogenic organisms[4]. We also recorded inflammation (redness) of the wound, stitch abscess, and discharge of culture negative fluid. These categories together with infected wounds were called inflamed wounds.

Differences between the two groups were compared using the χ^2 test.

Results

The two groups had similar preoperative and operative characteristics (*Table 1*). The length of the incision and depth of subcutaneous fat were similar. There was no difference in the time taken to create the wound in each group (*Table 1*).

There were 28 (11·6 per cent) inflamed wounds, of which 16 (6·7 per cent) were infected. Inflammation and infection were equally frequent in the two groups, independently of wound classification (*Table 2*).

Table 1 *Characteristics of patients and wounds studied*

	Scalpel	Diathermy
Number	130	110
Age (range)	68 (18–95)	72 (26–92)
Male:female ratio	60:70	43:67
Elective.emergency ratio	79:51	70:40
Incision		
Midline	86	67
Paramedian	15	9
Transverse	29	34
Length* (cm)	20 (16–33)	19 (15–22)
Depth* (cm)	2 (1·5–3)	2 (1·5–3)
Time* (min)	3·5 (2·8–4·5)	3·3 (2·5–4·5)

* Values are median (interquartile range)

Table 2 *Inflammation and wound infection by type of wound*

	Scalpel			Diathermy		
	Total	Inflamed	Wound infection	Total	Inflamed	Wound infection
Clean	23	2 (9)	1 (4)	27	1 (4)	0
Clean-contaminated	55	2 (4)	1 (2)	50	3 (6)	1 (2)
Contaminated	26	3 (12)	3 (12)	20	5 (25)	2 (10)
Severely contaminated ('infected')	26	8 (31)	6 (23)	13	4 (31)	2 (15)
Total	130	15 (11·5)	11 (8·5)	110	13 (11·8)	5 (4·5)

Values in parentheses are pecentages

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Two patients in the 'scalpel' group developed complete wound dehiscence. Both wounds were severely contaminated and developed wound abscesses prior to dehiscence.

Thirty-five incisions were made through a well healed previous laparotomy scar. Of these wounds 21 were made using a scalpel and 14 with the diathermy. There was no difference between these groups in time taken for incision or wound infection rate. There were two cases of accidental enterotomy, one in each group. The enterotomy was closed immediately and neither patient developed a wound infection or other complication.

Discussion

We have shown that the method of incision of a laparotomy wound has no effect on subsequent wound infection rates. There was no difference in the time required to make the incision and to achieve complete haemostasis. The more rapid haemostasis with diathermy appears to be counterbalanced by the more rapid incision of tissue with the knife.

Diathermy causes tissue necrosis in addition to division of the tissue[5], and this might favour infection or an inflammatory reaction around the wound[6,7]. The incidence of wound infection and of inflamed wounds was, however, similar in the two groups.

There were two burst abdomens but no significance can be attached to the fact that both incisions were made with a scalpel since in both overwhelming infection and chronic respiratory disease contributed to the dehiscence.

The 35 patients in whom the incision was made through a previously healed scar had similar characteristics to the overall series. Only one wound became inflamed.

It has been suggested that incisions made with diathermy might be less painful than those made with a scalpel[8]. If this is confirmed by others then there would be a positive reason for choosing the diathermy rather than a scalpel for incision of the abdominal wall. Until then each surgeon may follow his own personal preference.

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Clinical assessment and anorectal manometry before postanal repair: failure to predict outcome

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It has been suggested that preoperative measurement of resting anal canal pressure and internal sphincter function can be used to identify those patients with neurogenic faecal incontinence who are unlikely to benefit from the operation of postanal repair. We have therefore analysed the results of the operation in 62 patients (six men and 56 women, mean age 59 years, range 30–83 years) and related clinical outcome to preoperative assessment of: resting anal canal pressure, the presence of gape and a combination of gape and low resting pressure. None of these factors was found to predict a poor result after postanal repair.

Keywords: Postanal repair, faecal incontinence, anal sphincter

Postanal repair for idiopathic faecal incontinence is associated with a good result in approximately one-third of patients, some improvement in another third and no improvement in the remainder[1,2]. It is not clear which factors are responsible for determining the outcome of postanal repair. Previously it was felt that a successful operation depended on a reduction in the anorectal angle[3] but recent evidence suggests that a good result can be achieved independent of an alteration in the anorectal angle[4–6].

Some associate a successful postanal repair with an increase in anal canal pressure[1,4,7] but others find no significant change[5,6]. Some have demonstrated an increase in sphincter length in patients with a good result[1,5] while others have not confirmed this finding[4].

A number of patients must undergo surgery, therefore, who have only a slight chance of benefit. Continence is maintained by the external sphincter, the condition of the internal sphincter, which produces most of the resting anal tone, and the state of anorectal sensation. We therefore examined the results achieved by postanal repair in a group of patients subdivided according to clinical and physiological parameters of preoperative internal sphincter function.

Patients and methods

Between 1985 and 1987 62 patients underwent postanal repair at St Mark's Hospital, London. There were six men and 56 women with a mean age of 59 years (range 30–83 years). Each patient underwent proctosigmoidoscopy and digital examination before operation and a subjective clinical assessment of the anus with respect to gape was made Gape was defined as opening of the anus with gentle retraction of the perianal skin

Anorectal manometry[8] was performed before operation and patients were divided according to the value of the resting pressure into ten groups. 0–10 cmH_2O, 11–20 cmH_2O, 21–30 cmH_2O etc The median value was between 30 and 40 cmH_2O and a more even distribution was obtained by setting the reference point at 30 cmH_2O rather than 40 cmH_2O The reference point of 30 cmH_2O was therefore arbitrarily chosen in order to separate the patients into two groups

The clinical result of the procedure was objectively assessed as excellent if the patient had achieved normal continence, fair if the patient was continent of solid stool only and poor if the patient remained incontinent of stool and flatus.

Results

Amongst the whole group an excellent result was achieved in 28 patients (45 per cent), a fair result in 23 (37 per cent) and a poor result in 11 (18 per cent)

Resting pressure

Details of preoperative anorectal physiology were available in 45 patients and these were arbitrarily divided into two groups as described above – those with a resting pressure >30 cmH_2O (group A) and those with a resting pressure $\leqslant 30$ cmH_2O (group B). There were 19 patients in group A (one man and 18 women, mean age 58 years, range 37–79 years) and 26 in group B (three men and 23 women, mean age 58 years, range 30–83 years).

Table 1 shows the clinical results of postanal repair in these patients and demonstrates no difference between the two groups. Preoperative resting anal canal pressure is not related to outcome after postanal repair.

Presence of gape

Subjective clinical assessment of the anus with respect to gape was made in 59 patients who subsequently underwent postanal repair. Gape was present in 31 patients (two men and 29 women, mean age 60 years, range 35–83 years) and absent in 28 (four men and 24 women, mean age 57 years, range 30–76 years).

Table 2 shows the clinical results of postanal repair and demonstrates no significant difference between the two groups. The presence of gape before operation is not related to outcome after postanal repair.

Gape and pressure

The patients were divided into two groups – those with a gaping anus and a resting pressure $\leqslant 30$ cmH_2O (group A) and those with a resting pressure >30 cmH_2O and no gape (group B). There were 14 patients in group A (two men and 12 women, mean age 58 years, range 37–79 years) and 16 in group B (three men and 13 women, mean age 55 years, range 30–76 years).

Table 1 *Effect of pressure*

Clinical result	No. of patients with resting pressure $\leqslant 30$ cmH_2O before operation	No of patients with resting pressure >30 cmH_2O before operation
Excellent	9 (47)	12 (46)
Fair	7 (37)	9 (35)
Poor	3 (16)	5 (19)
Total	19	26

Values in parentheses are percentages Excellent *versus* poor, $P = 1{\cdot}14$, not significant (Fisher's exact test)

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Table 2 *Effect of gape*

Clinical result	No. of patients with gape	No. of patients without gape
Excellent	16 (52)	10 (36)
Fair	10 (32)	12 (43)
Poor	5 (16)	6 (21)
Total	31	28

Values in parentheses are percentages. Excellent *versus* poor, $P=0·59$, not significant (Fisher's exact test)

Table 3 *Effect of gape and pressure*

Clinical result	No. of patients with gape and pressure $\leqslant 30$ cmH$_2$O	No of patients with no gape and pressure >30 cmH$_2$O
Excellent	6 (43)	5 (31)
Fair	5 (36)	8 (50)
Poor	3 (21)	3 (19)
Total	14	16

Values in parentheses are percentages. Excellent *versus* poor, $P=1·25$; not significant (Fisher's exact test)

Table 3 shows the clinical results of postanal repair and demonstrates no significant difference between the two groups. The combination of gape and a low resting pressure is not related to outcome after postanal repair.

Discussion

The internal anal sphincter has been shown to be histologically[9] and physiologically[10] abnormal in some patients with idiopathic faecal incontinence. The response of isolated strips of internal sphincter muscle exposed to various drugs in an organ bath has also been shown to be abnormal[8]

Poor internal anal sphincter function (defined clinically, manometrically or by a combination) does not help identify a group of patients who are unlikely to be helped by postanal repair. This observation contrasts with that of Yoshioka *et al.*[6] who investigated 19 patients before and 3 months after postanal repair and found that the seven patients who did not benefit could be detected before operation by a combination of radiological and physiological tests. Their technique of postanal repair employs absorbable sutures of 00 Dexon® (Davis and Geck, Gosport, UK)[2] in contrast to the practice at St. Mark's Hospital where non-absorbable materials have been used throughout. Their 3-month follow-up may be rather short. In this study the minimum follow-up was 1 year with a range between 1 and 3 years. These findings suggest that operations designed to help internal sphincter tone in patients with idiopathic faecal incontinence are unlikely to be of much benefit.

Anorectal sensation seems to play a central role in the maintenance of continence and there is clear evidence of a sensory abnormality in patients with idiopathic faecal incontinence[11,12]. There are some patients without evidence of a pudendal neuropathy in the external anal sphincter who suffer minor degrees of faecal incontinence and whose rectal sensation is dulled[13] Perhaps impaired anorectal sampling[14] may be more important than actual sphincter function in the genesis of incontinence[15,16] A successful outcome after postanal repair is associated with an improvement in anal canal sensation assessed by mucosal electrosensitivity[4,17] In patients who have a good functional result after postanal repair the beneficial effect may be due to drawing skin with better sensation up into the anal canal thereby improving sampling. If this is so there are simpler ways of achieving the same result than by performing a postanal repair.

Besides sensation and sphincter function, rectal contractility may vary between patients and help to determine which patients are likely to do well after postanal repair. Ambulatory techniques might help to identify patients.

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Comparison of Coloscreen Self-Test® and Haemoccult® faecal occult blood tests in the detection of colorectal cancer in symptomatic patients

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The usefulness of faecal occcult blood tests is limited by their acceptability to patients. Standard tests require the collection of a stool sample which may inhibit compliance. Self-read tests which avoid this step have therefore been devised. Coloscreen Self-Test® (CST) and Haemoccult®, which may be regarded as the standard slide test, were offered to 450 consecutive patients attending surgical outpatient clinics with symptoms suggestive of lower gastrointestinal disease. Both tests were successfully completed by 383 patients. Although 262 (68 per cent) patients indicated that they preferred CST this was not reflected in the overall compliance to the two tests (CST 86 per cent, Haemoccult 90 per cent). CST gave a positive result in only eight out of 24 patients with a colorectal cancer (sensitivity = 33 per cent) compared with 13 out of 24 for Haemoccult (sensitivity = 54 per cent). CST had no advantage from increased compliance to outweigh its lower sensitivity.

Keywords: Faecal occult blood test, screening, colorectal cancer

Faecal occult blood tests are being used increasingly as a means of screening for colorectal neoplasia[1]. A major factor in the success of a screening programme is the acceptability of the test as only those who are prepared to complete the test can benefit from the screening programme. Conventional slide tests suffer the disadvantage of requiring the subject to collect a small sample of faeces and apply this to the test card which has then to be delivered to the screening centre. Compliance rates of 50–70 per cent have been reported in screening studies using slide tests[2,3].

In an attempt to improve the acceptability of faecal occult blood testing, tests have been developed which do not require the collection of a faecal sample. The test cards are simply dropped into the toilet after a stool has been passed and a change in colour of an indicator patch may be observed in the presence of occult blood. Unlike the slide tests, these floating card tests rely on blood on the surface of the stool being washed off as it enters the water so forming a surface film of blood on which the test card floats.

The purpose of this study was to compare one such test (Coloscreen Self-Test) with an established slide test (Haemoccult) in a group of symptomatic individuals to assess the likely value of a self-read test in population screening.

Patients and methods

A total of 450 consecutive patients attending the surgical outpatient departments with symptoms suggestive of lower gastrointestinal disease were asked to complete both a Coloscreen Self-Test (Cambridge Selfcare Diagnostics Limited, Newcastle upon Tyne, UK; CST) and a Haemoccult (Haemoccult, Rohm Pharma GmbH, Darmstadt, FRG) test over a 3-day period

The patients noted any colour change in the indicator patches of the CST and recorded them on the result card. Samples were then taken for the Haemoccult test. At the end of the 3-day period the three Haemoccult slide cards and the CST result cards were returned Patients were also asked to indicate which of the two tests they preferred. The Haemoccult slides were read by laboratory staff and the results recorded together with those of the CST.

All patients underwent full colonic investigation using either colonoscopy or double contrast barium enema and flexible fibreoptic sigmoidoscopy.

Results

Both tests were successfully completed by 383 out of 450 patients. CST was completed by 387 (86 per cent) patients and Haemoccult by 404 (90 per cent) patients. Of those who completed both tests 262 (68 per cent) preferred the CST and 45 (12 per cent) preferred Haemoccult. The remainder expressed no preference (*Table 1*).

In the group of 383 patients who completed both tests there were 30 (8 per cent) positive CST results and 44 (11 per cent) positive Haemoccult results (*Table 2*). Of a total of 24 cancers diagnosed in this group, eight were detected by CST (sensitivity

Table 1 *Preference of 383 patients for Coloscreen Self-Test or Haemoccult*

Preference	No ($n = 383$)
Coloscreen Self-Test	262 (68)
Haemoccult	45 (12)
No preference	76 (20)

Values in parentheses are percentages

Table 2 *Coloscreen Self-Test and Haemoccult results in 383 patients with lower gastrointestinal symptoms*

Test results	No. of patients	No. of cancers
Haemoccult positive/CST positive	18	6
Haemoccult negative/CST positive	12	2
Haemoccult positive/CST negative	24	7
Haemoccult negative/CST negative	323	9
Haemoccult positive/CST uncertain	2	0
Haemoccult negative/CST uncertain	4	0
Total	383	24

CST, Coloscreen Self-Test

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Table 3 *Location of colorectal carcinoma detected by Coloscreen Self-Test and Haemoccult faecal occult blood tests in symptomatic patients*

Site of cancer	No.	CST positive ($n=30$)	Haemoccult positive ($n=44$)
Rectum	14	8	8
Sigmoid	5	–	2 (+2)*
Transverse	1	–	1
Ascending	1	–	–
Caecum	3	–	2
Total	24	8	13 (+2)*

CST, Coloscreen Self-Test. *Additional figures for those who completed only the Haemoccult test

33 per cent) and 13 by Haemoccult (sensitivity 54 per cent) and their sites are given in *Table 3*. There were an additional three cancers detected in patients who completed only one of the tests. Two of the cancers were in the Haemoccult only group and both had a positive test result, and one was in the CST only group and the test result was negative. A positive CST result was associated with colorectal cancer in eight (27 per cent) of 30 instances compared with 13 (30 per cent) of 44 instances for Haemoccult.

Discussion

Although patients preferred to perform the test that did not require collection of a stool sample, compliance to the test requiring such collection was a little higher than to the self-read test. A similar finding has recently been reported in a pilot population screening study comparing CST and Haemoccult[4].

CST failed to detect any of the ten colonic cancers and identified only eight of the 14 rectal cancers. Seven of these eight cancers had been associated with frank rectal bleeding.

Haemoccult not only detected 13 of the 24 cancers in those who completed both tests correctly, but also a further two tumours in patients who failed to complete the CST. The Haemoccult test alone detected 15 (58 per cent) out of 26 cancers, which is similar to reported figures[1].

Failure of a self-read test to identify occult bleeding may be due either to failure of the chemical test itself or to misreading of the test by the patient. However, it is the performance of the test as a whole which must be assessed and the poor sensitivity of this particular self-read test is unacceptably lower than that of an established slide test On these grounds alone it is unsuitable as a test for asymptomatic population screening.

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Rectopexy for internal rectal intussusception

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Twelve patients presented with symptomatic internal intussusception of the rectum between 1979 and 1987. All were women with a mean age of 55·5 years. Ten patients had symptoms of obstructed defaecation and only three were completely continent. Polyvinyl alcohol sponge abdominal rectopexy was performed in each patient. Over a mean follow-up period of 26·9 months there was no recurrence of internal intussusception. The functional results, however, were mixed but only one patient remained incontinent for solid stool. Rectal discomfort and defaecatory difficulties persisted; six patients continued to strain at stool and in three this was worsened by the operation. Abdominal rectopexy can be recommended for those with associated incontinence, significant rectal bleeding or solitary rectal ulcer but may not benefit those who have obstructed defaecation.

Keywords: Intussusception, rectum, rectopexy

Complete rectal prolapse is a well recognized condition and results following abdominal rectopexy are generally good with a recurrence rate of less than 5 per cent[1–4] and functional improvement, particularly for continence[2–4]. By contrast internal intussusception of the rectum is frequently overlooked although the presenting features have been clearly described[5–8]. With the exception of a series of articles from Sweden[7–11] there have been few reports of the management of this condition[5,12] and practically none that have detailed the functional outcome of surgery.

Between 1979 and 1987 12 patients underwent polyvinyl alcohol sponge abdominal rectopexy for symptomatic internal intussusception of the rectum. The clinical features, diagnostic investigations and the response to surgery are described with particular emphasis on functional outcome.

Patients and methods

Between June 1979 and November 1987 12 patients underwent abdominal rectopexy as treatment for internal rectal intussusception. All patients were seen and re-examined in the out-patient department and 11 answered a detailed questionnaire about rectal function. The mean follow-up period was 26·9 months.

Clinical features

All patients in the series were women with a mean age of 55·5 years. Three had undergone hysterectomy and two had had a previous pelvic repair; two patients had undergone both procedures. Local anorectal operations had been carried out in five patients. One patient had had a transverse colostomy for incontinence and another had had a previous sigmoid colectomy for diverticular disease.

The most common symptom, straining at stool, was seen in seven patients. Six patients complained of incomplete rectal emptying, six of rectal pain and five of rectal bleeding or mucus. Only three patients were fully continent (grade 1); one was incontinent for flatus (grade 2), five for liquid stool (grade 3) and three for solid stool (grade 4). No distinction was drawn between occasional or regular incontinence. Ten patients had an abnormal bowel habit, five complained of faecal frequency, three were constipated and two had alternating constipation and diarrhoea.

Investigations

On sigmoidoscopic examination whilst straining in the left lateral position an internal intussusception was noted in ten patients by measuring the sigmoidoscope descent while the examiner kept the instrument fixed on a constant piece of rectal mucosa. The minimum sigmoidoscopic descent to make the diagnosis was 3 cm. In two patients a solitary rectal ulcer was seen and in another two the features of proctitis or gross perineal descent were noted. In a further two patients a solitary rectal ulcer was noted when internal intussusception was not clinically apparent.

Defaecating proctography was performed in eight patients. In the two patients with a solitary rectal ulcer but no obvious sigmoidoscopic intussusception the proctogram revealed intussusception. The other six patients investigated had a clinical diagnosis of internal intussusception. In three patients the diagnosis was confirmed by proctography; in one there was anterior enfolding of the rectum but no circumferential intussusception and in two there was perineal descent alone.

Anorectal manometry was carried out in nine patients. Both resting anal pressure and maximal squeeze pressure were lower in the incontinent patients (mean 58·3 (range 20–90) cmH$_2$O) and 67·1 (range 20–140) cmH$_2$O respectively) compared with those who were continent (mean 96 (range 48–120) cmH$_2$O and 88·3 (range 20–200) cmH$_2$O respectively).

Operative details

Abdominal rectopexy was performed via a midline incision and the upper half of the lateral ligaments were divided during rectal mobilization. The polyvinyl alcohol sponge was sutured to the presacral fascia and was then attached to the mobilized and straightened rectum to encompass two-thirds of the circumference. In the seven patients with a uterus ventrofixation was performed by placing a non-absorbable suture around each round ligament, the suture was then passed through the abdominal wall and tied anterior to the anterior rectus sheath holding the uterus in an anteverted position. The rectovaginal pouch was reconstituted with two rows of absorbable sutures.

Results

There was no mortality and no immediate morbidity. Two patients developed late postoperative problems related to the rectopexy; one developed severe constipation requiring a colostomy 16 months later and one developed a postrectal abscess which was drained endorectally 4 years after the operation[13].

There has been no recurrent intussusception and three out of four solitary rectal ulcers healed.

Six patients continued to strain at stool and in three this was worse than before the operation (*Table 1*). The sensation of incomplete evacuation improved and persisted in only one patient. Rectal discomfort did not seem to be affected by the procedure. A normal bowel habit without laxatives was achieved in only three patients with one patient requiring senna. Four patients were constipated and four continued to complain of faecal frequency. Six still needed laxatives or suppositories. Continence improved in four but deteriorated slightly in one. Better control was achieved in two of these at the expense of increased constipation and straining. Preoperative manometry

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Table 1 *Preoperative and postoperative symptoms*

	Preoperative symptoms				Postoperative symptoms			
Patient no.	Grade of continence	Bowel habit	Other defaecatory symptoms	Rectal discomfort	Grade of continence	Bowel habit	Other defaecatory symptoms	Rectal discomfort
1	3	Normal	Straining Incomplete emptying	Yes	3	Constipated	Straining worsened	Yes
2	1	Constipated	Straining	No	2	Normal	None	No
3	4	Normal	None	No	3	Normal	None	No
4	3	Faecal frequency	None	No	3	Faecal frequency	None	Yes
5	1	Faecal frequency	Straining Incomplete emptying	Yes	1	Constipated	Straining persisted	No
6	4	Faecal frequency	None	Yes	4	Faecal frequency	Straining developed	Yes
7	3	Variable	Straining Incomplete emptying	Yes	1	Constipated	Straining worsened	Yes
8	3	Faecal frequency	Incomplete emptying	Yes	3	Faecal frequency	None	Yes
9	4	Constipated	Straining	No	1	Constipated	Straining worsened	Yes
10	3	Variable	Straining Incomplete emptying	No	3	Normal	None	No
11	1	Constipated	Straining	No	1	Normal	None	No
12	2	Faecal frequency	Incomplete emptying	Yes	2	Faecal frequency	Straining developed Incomplete emptying	No

was not of predictive value in determining the patients whose continence would improve. Rectal bleeding ceased in all but one patient.

Overall, eight patients felt they had benefited from the operation, one felt she had deteriorated and two were unchanged. This information was not available for the other patient in the series.

Discussion

The clinical condition of internal intussusception of the rectum has been recognized since the early part of this century[14]. Swedish workers[7–9] have clearly described the clinical features in a series of 292 patients. The commonest symptom of obstructed defaecation was found in 57 per cent, complete or partial incontinence was noted in 46 per cent, rectal pain in 43 per cent and rectal bleeding in 27 per cent. This symptom complex confirmed the findings of previous workers[5,6,12]. Our patients complained of the same symptoms but the incidence of complete or partial incontinence was higher at 75 per cent and rectal bleeding was seen in 42 per cent.

Of 224 patients seen at a rectal clinic 13 (6 per cent) had rectal intussusception; by comparison only four (2 per cent) had complete rectal prolapse[7]. Despite this and the fact that obstructed defaecation is a relatively common complaint, the diagnosis of rectal intussusception is infrequently made, possibly owing to a failure to elicit the intussusception during the clinical examination. Asman was the first to describe rectal invagination if the patient strains as the sigmoidoscope is withdrawn[5]. The intussusception will be palpable in 38 per cent of patients on digital examination during straining and on sigmoidoscopy 23 per cent have abnormal findings such as ulceration or traumatic proctitis which should alert one to the diagnosis[7]

Broden pioneered the technique of cineradiography in internal intussusception[15] and Bartolo *et al.* demonstrated significantly more perineal descent and greater increase in the anorectal angle on straining in patients *versus* controls[16]. Hoffman *et al.* studied 30 patients with a history of obstructed defaecation of unknown cause[10] and in 26 patients (87 per cent) either complete rectal prolapse or intussusception was demonstrated.

The management of patients with rectal intussusception can be difficult. Conservative management with laxatives, suppositories or enemas produced an improvement in 34 per cent, a deterioration in 20 per cent and no change in 46 per cent[8], predictably incontinence worsened. In the same series 63 patients underwent Ripstein rectopexy for obstructed defaecation, incontinence, solitary rectal ulcer or bleeding. Although incontinence improved in 23 out of 29 patients (79 per cent) evacuation improved in only 12 out of 23 (52 per cent) and worsened in eight out of 23 (35 per cent). In contrast Asman performed rectopexy and sigmoid resection in ten patients with no recurrences; eight patients obtained complete or marked relief of their symptoms[5]. Ripstein also reports good results with symptomatic relief in 11 out of 12 patients following his eponymous operation[12].

Our results are less encouraging although two-thirds felt that they had improved. There was improvement in two-thirds of those with incontinence for solid stool, although half continued to strain and discomfort persisted. The sensation of incomplete evacuation was much improved and the bleeding due to traumatic proctitis subsided.

This is possibly the first series to have reported the Wells procedure in internal intussusception alone[17] In rectopexy for complete rectal prolapse the incidence of faecal impaction and constipation is higher after the Ripstein procedure[1,18] than the Wells operation[2,19]. Many of our patients had a pre-existing functional bowel disorder and although the rectopexy restored the anatomy and prevented intussusception the bowel dysfunction remained.

Many of the symptoms described above resemble those found in the descending perineum syndrome[20]. There is more descent compared with controls but this is not inevitably present and was measured in only three out of seven patients in this study There are also similarities with the solitary rectal ulcer syndrome, in which coexisting internal intussusception or complete rectal prolapse is found in between 16 and 66 per cent of cases[21–24].

Good results with a 90 per cent ulcer cure rate have been reported following rectopexy for associated solitary rectal ulcer and prolapse[25] The complex relationship between rectal intussusception, solitary rectal ulcer and the descending perineum has yet to be fully disentangled.

Johansson *et al.* have suggested that incontinence in rectal intussusception is an indication for rectopexy as two of their patients had progressive incontinence on medical therapy and incontinent patients improved after surgery[8]. Many of these patients are chronic strainers, often with perineal descent[16]. Several observers have shown that this may lead to a pudendal neuropathy and sphincter denervation[26,27] or inhibition of the pelvic floor[28]. Pudendal neuropathy is known to be potentially reversible following the stretching of childbirth[29] and recovery may occur following anatomical restoration by rectopexy The intussusception may have an effect upon the internal sphincter as anal dilatation has been shown to reduce resting anal pressure[30]. Following Ripstein rectopexy for intussusception Broden *et al.* have shown an elevation in the resting anal pressure[31]. Better continence cannot be ascribed to an improvement in the anorectal angle as this is straightened by rectopexy[32].

Broden and Snellman demonstrated that complete rectal prolapse begins as an internal intussusception 6–8 cm above the anal verge[15]. Over 2 years only two of their patients developed complete rectal prolapse so rectopexy cannot be recommended prophylactically. It appears useful in improving control of the incontinent patient, in those with a solitary rectal ulcer or in those with troublesome bleeding. The results may be disappointing and the patient should be informed of what rectopexy can achieve before agreeing to surgery.

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Perineal, vulval and vaginoperineal reconstruction using the rectus abdominis myocutaneous flap

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Poor perineal healing is a major complication of total or partial pelvic exenteration especially when the pelvis and perineum have previously been irradiated. Perineal, vulval or vaginoperineal reconstruction was performed in five women using the inferiorly based rectus abdominis myocutaneous flap. Primary perineal wound healing occurred in all patients and no flap-related complications developed. Primary healing of abdominal wall wounds occurred in all patients without incisional hernia. Three of the patients had an anterior or total pelvic exenteration with continent urinary diversion by the Mitrofanoff technique. Two of the patients had complete vaginal reconstruction and one patient had after-loading catheters inserted for postoperative interstitial irradiation. The patients were in hospital for 42, 28, 21, 17 and 15 days respectively. The longest stays were associated with training for self-catheterization of the continent urinary diversion. Median follow-up was 9 months. One patient developed two perineal recurrences at 16 months which were resected, and she remains disease-free 6 months later.

Keywords: Perineum, vagina, vulva, reconstruction

Various pelvic exenterations are commonly performed to treat a variety of malignant conditions, mostly persistent or recurrent tumours of the pelvic organs, collectively referred to as cloacogenic malignancies[1]. Less common indications for pelvic exenteration include extensive perineal radiation damage[2], extensive perineal fistulae and certain post-traumatic injuries[3]. Following such extensive surgery, particularly when radiotherapy has been part of the initial management, delayed wound healing is a problem that can result in considerable morbidity and a protracted hospital stay. Primary wound healing is often not achieved[4–6] and a persistent perineal sinus may prove to be a problem[7,8].

The rectus abdominis myocutaneous flap has previously been used, when superiorly based, for the repair of chest wall defects and breast reconstruction[9,10] and, when inferiorly based, for the repair of groin[11] and perineal defects[12], and for the treatment of persistent perineal sinuses[13]. This paper describes the use of an inferiorly based myocutaneous flap to establish primary healing of large perineal wounds following excision of diseased and irradiated tissues The skin pedicle was used to reconstruct the perineum and posterior vaginal wall of two patients, the perineum alone in two patients, and the vulva and perineum of one patient. The bulk of the muscle and subcutaneous fat was used to reduce the dead space of the pelvic cavity

Patients and methods

Two patients aged 59 and 60 years respectively had been treated for carcinoma of the anus by extensive irradiation. One of them was referred with recurrent adenocarcinoma in the anus and rectovaginal septum following external beam radiotherapy The other had no recurrence of squamous carcinoma following external beam and interstitial radiotherapy, but was referred with severe perineal pain controlled only by diamorphine A defunctioning pelvic colostomy had been performed for incontinence resulting from radiation damage to the sphincter and perineum. Both patients were treated by extended abdominoperineal resection of rectum and anus including perineal skin and posterior vaginal wall up to the posterior fornix The rectus abdominis myocutaneous flap was used to reconstruct the vagina and perineum

Two patients aged 58 and 63 years respectively were referred, following abdominoperineal resection and radiotherapy, with recurrent adenocarcinoma of the rectum invading the vagina and bladder (*Figure 1*) They were treated by total pelvic exenteration Both had continent Mitrofanoff urinary diversions. One of these patients had, in addition, total vaginal reconstruction with pedicled ileum and the other required peroperative placement of after-loading catheters to the pelvic side wall, where clearance of disease was considered to have been inadequate. The perineum was reconstructed using the rectus abdominis myocutaneous flap

One patient aged 56 years was referred with extensive postirradiation recurrent squamous carcinoma of the anterior vaginal wall invading the bladder base, vulvae and clitoris. She was treated by anterior exenteration and simple vulvectomy. Reconstruction was by Mitrofanoff urinary diversion, pedicled loop of colon for vagina and rectus abdominis myocutaneous flap for perineum and vulva.

After mechanical bowel preparation and under systemic antibiotic cover the patients were put in the Lloyd-Davies position. The abdomen was explored through an infraumbilical midline incision. Following the surgical resection an inferiorly based rectus abdominis myocutaneous flap was raised taking care to preserve the inferior epigastric vessels which lie on its deep surface[14]. The length and breadth of the skin pedicle varied according to the size of the perineal, vulval or vaginoperineal defect Primary closure of the abdominal wall was achieved in all cases The rectus muscle was transected at the level of the costal margin and the superior epigastric vessels were ligated. The myocutaneous flap was then rotated through 180° on its inferior vascular pedicle and transferred through the pelvis into the perineum and the cutaneous island inset. In the one patient where the myocutaneous flap was used for vulval reconstruction, the pedicle was transposed suprapubically. Care was taken during the handling of the flap to avoid shearing the small perforating vessel between the muscle and the overlying skin. Viability of the flap was verified by palpating the pulsatile vascular pedicle and by observing capillary refill after blanching

Patients requiring continent urinary diversion had a Mitrofanoff-type reconstruction A urinary reservoir was formed from an isolated segment of caecum and ascending colon. Intestinal continuity was re-established by ileotransverse anastomosis The isolated colon was detubularized to reduce intrinsic peristaltic contractions. The appendix, mobilized on its pedicle and with the distal tip resected, was implanted into the reservoir in a 4-cm submucosal tunnel. The other end of the appendix was brought to the skin and formed a continent catheterizable stoma. The ureters were implanted in submucosal tunnels at a suitable site in the pouch[15]

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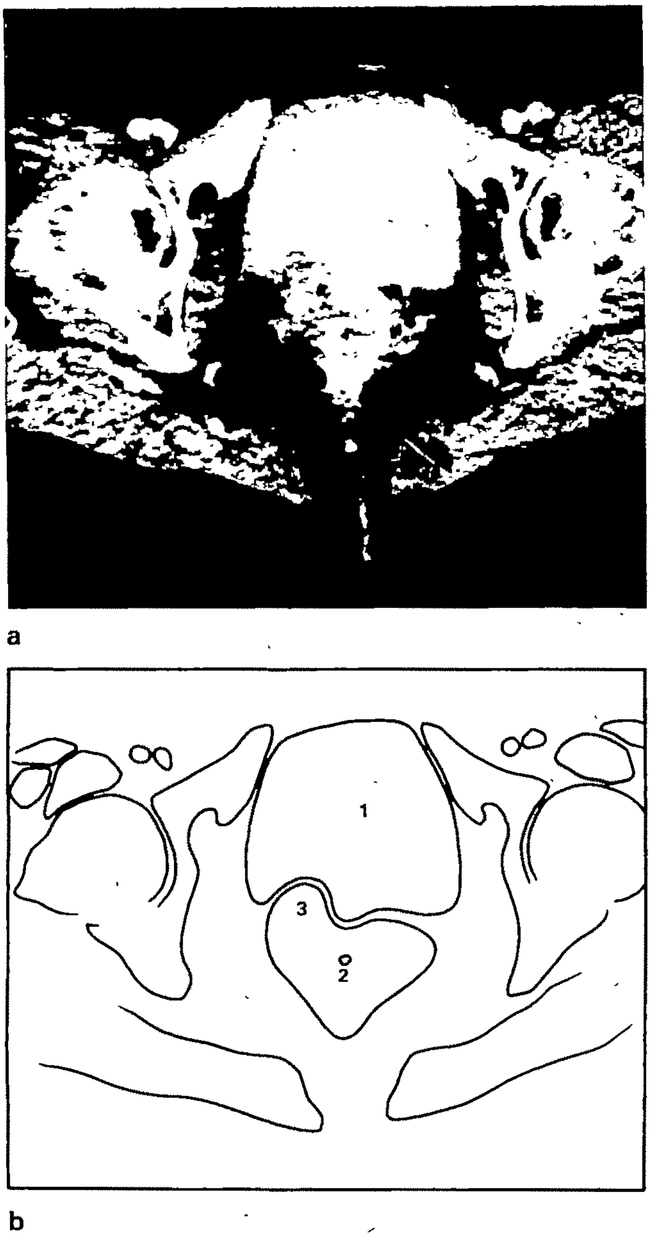

Figure 1 *Computed tomogram,* **a**, *and line drawing,* **b**, *showing recurrent carcinoma of rectum (after abdominoperineal resection of rectum) at level of vaginal vault invading right side of bladder base 1, Bladder, 2, vaginal vault/cervix uteri, 3, recurrent carcinoma*

When patients were having simultaneous posterior vaginal wall reconstruction, the anterior lip of the flap was reflected into the pelvis and sutured to the posterior vaginal wall remnant (*Figures 2* and 3). Closure of the large perineal defects was thus achieved. The bulk of the myocutaneous flap contributes to the filling of the pelvic cavity. Corrugated drains were placed in the pelvis and brought out through the perineal wound.

Results

Primary healing of both donor and perineal wounds was achieved in all cases. One patient required 6 days' ventilation after operation due to chest complications but this did not prejudice flap healing. The abdominal defects closed primarily in all patients and none has incisional hernia. Hospital stay was 42, 28, 21, 17 and 15 days respectively, the longer admissions being related to Mitrofanoff training. One patient treated for recurrent carcinoma of the rectum developed two perineal wound recurrences at 16 months. These were excised following uneventful mobilization of one edge of the flap and she remains well and disease-free 6 months later. The three patients who had internal urinary diversions are continent and practise intermittent clean self-catheterization every 4–6 h by day and occasionally at night. There have been no urinary tract complications.

Discussion

Securing primary healing of perineal wounds remains a challenging surgical problem, particularly after radiotherapy[16]. Healing difficulties are compounded by haematoma and sepsis within the unobliterated pelvic cavity. Initial techniques of abdominoperineal resection resulted in granulating cavities and protracted healing[17]. In an attempt to improve this situation Crile and Robnett described closure of the pelvic peritoneum and perineal skin with efficient drainage of the dead space[18] and Papaionnou described closure of the perineal skin only, allowing small bowel freely to enter the pelvis[19]. Despite these measures Irvin and Goligher found that 17–35 per cent of perineal wounds were not healed at 6 months[6]. The transfer of pedicled omentum to obliterate the pelvic cavity has contributed to healing[4] but this useful organ varies considerably in size and previous surgery or secondary deposits can render it unusable.

The intrinsic benefits of a myocutaneous flap are considerable. The transfer of a muscle with its own blood supply facilitates wound healing[9]. This improvement may be the result of improved delivery of nutrients, oxygen, inflammatory cells

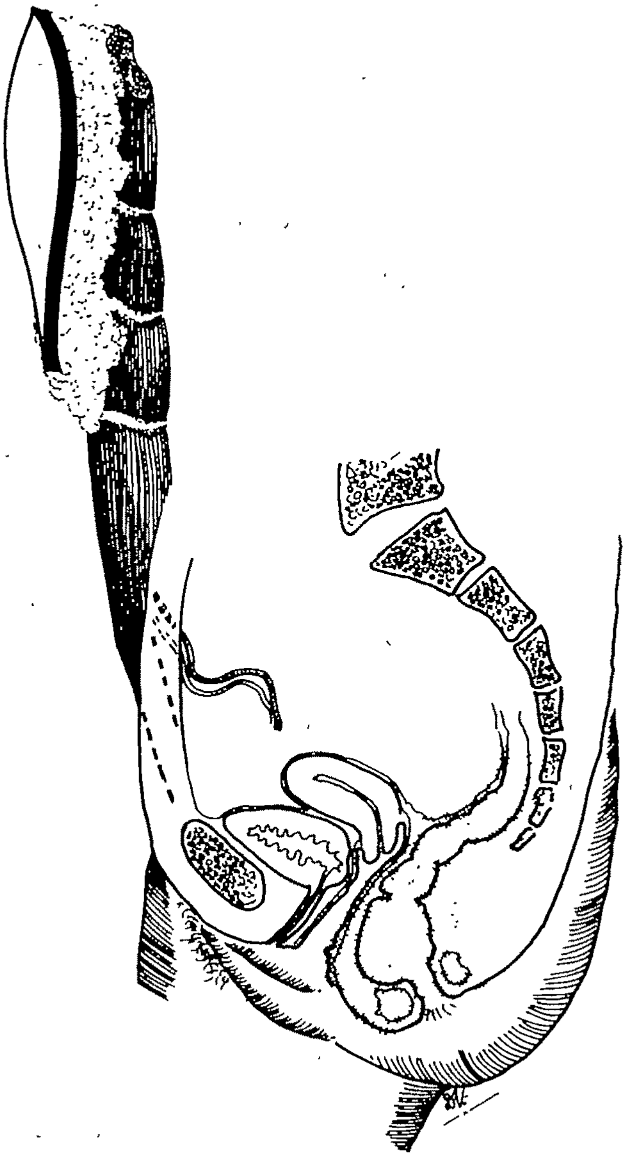

Figure 2 *Sagittal section of pelvis and abdomen showing the raising of the rectus abdominis myocutaneous flap.* ▢, *Volume to be resected*

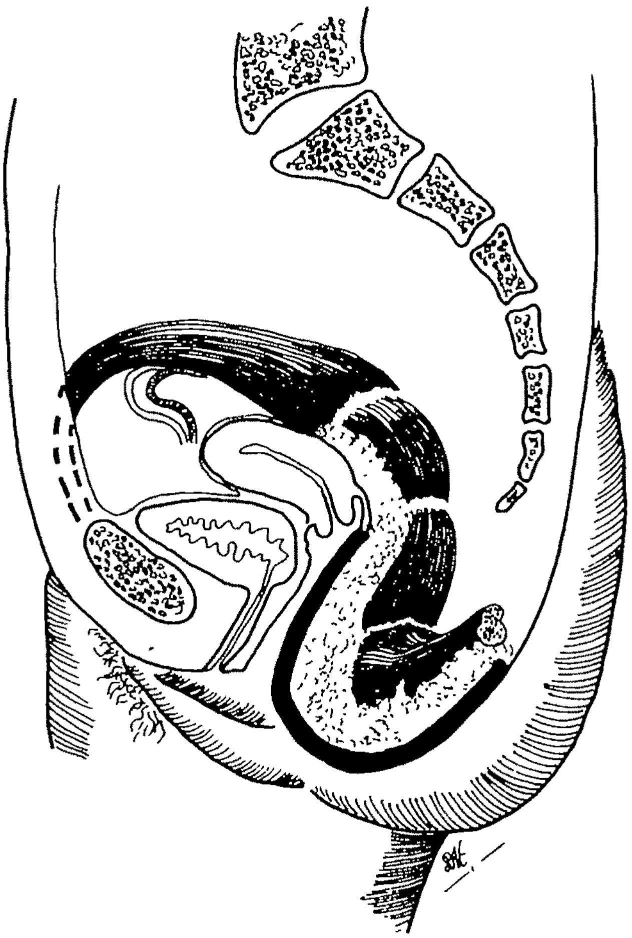

Figure 3 *Sagittal section of the pelvis showing the reflection of the myocutaneous flap to reconstruct the vagina and perineum*

and antibiotics to the wound[20], which is particularly important in the healing of heavily irradiated tissues.

The gracilis myocutaneous flap has been well described for reconstruction of perineal defects[2,3,21,22]. Its disadvantages include a limited skin paddle size and a variable blood supply. Occasionally the dominant blood vessels enter the muscle as low as the mid thigh, limiting the length of the pedicle and its access to the perineal defect[14]. For large perineal defects, bilateral gracilis flaps may have to be raised

In contrast, the inferior epigastric vessels provide the rectus abdominis myocutaneous flap with a consistent and excellent blood supply[14]. Furthermore, a large skin paddle is available for reconstruction. A long pedicle allows the flap to be transposed with little risk of tension or kinking of the feeding vessels. The skin island is therefore capable of filling large defects in the perineum and is particularly useful for reconstruction when wide excision of radiation-damaged perineal tissues has been performed.

When the bladder is removed it is conventional to form an ileal conduit. A continent internal diversion adds considerably to the length of surgery and may potentially cause major complications, but it is offered to all patients having anterior or pelvic exenteration who are physically and emotionally fit enough. Many methods are available which differ only in detail. In the patients described, available viscera were used to form a reservoir. The Mitrofanoff technique of submucosal tunnelling of a narrow tube, such as the appendix, into the pouch to give continence was used as the Kock nipple has been found to be rather unreliable[15,23].

The rectus abdominis flap for perineal, vulval and vaginoperineal reconstruction following radical resection of tumours from heavily irradiated beds has been described. When anterior or total pelvic exenteration is necessary, further refinement by continent urinary diversion and vaginal reconstruction may be added Primary healing may be expected and flap-related complications are rare.

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Epidural analgesia in colonic surgery: results of a randomized prospective study

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Colonic surgery patients were studied to measure: the influence of continuous thoracic epidural analgesia (TEA) on a postoperative pain score, the time till onset of defaecation, blood loss, postoperative temperature elevations, rate of bacterial contamination of wounds and urine, and general surgical complications. Group I patients (n = 57) *received general anaesthesia and TEA for the operation, followed by continuous TEA (0·25 per cent bupivacaine) for 72 h. Group II patients* (n = 59) *received general anaesthesia for the operation, followed by systemic analgesia on request. Significant beneficial effects of TEA in group I were demonstrated by lower pain scores in the first 24 h after surgery and earlier defaecation. However, there were fewer temperature elevations in group II. There was no significant difference between the groups in terms of positive bacteriological cultures, blood loss, need for postoperative mechanical ventilation and complications. However, there was a trend toward a higher rate of rectal anastomotic breakdown, increased blood replacement and intensive care therapy, and longer hospitalization in group I. These results do not suggest any significant beneficial therapeutic effect of continuous TEA in colonic surgery compared with a conventional systemic analgesic regimen. In selected patients (i.e. those with severe pain or those prone to develop postoperative ileus) continuous TEA may be beneficial.*

Keywords: Colonic surgery, continuous epidural analgesia, postoperative morbidity

Major abdominal surgery patients receiving continuous epidural analgesia during the postoperative period have shown early defaecation, rapid mobilization and a relatively short stay in hospital[1–4]. Although numerous reports describe the advantages of this anaesthetic technique, only a few studies involve specifically colonic surgery[2,3]. Reliable data on the influence of epidural analgesia on postoperative morbidity in such patients are not available[3]. To validate the hypothesis that colonic surgery patients benefit from continuous thoracic epidural analgesia (TEA), a prospective open randomized study has been carried out.

Patients and methods

The study was conducted from 1 June 1986 to 30 November 1987. During this period 178 patients had major abdominal surgery with either colonic resection and/or anastomosis. Only patients classified as American Society of Anaesthesiology (ASA) category I, II or III and who gave their informed consent were included. Written treatment protocols were used for both patient groups. This included postoperative pain management.

Randomization was performed by allotting patients having surgery on odd numbered days to the group receiving TEA plus general anaesthesia (group I, $n = 57$) while patients scheduled for surgery on even days received general anaesthesia without epidural block (group II, $n = 59$). Both groups were comparable in terms of preoperative morbidity and medication as well as operative procedures and surgeons (*Table 1*).

Sixty-two patients were excluded from the study for various reasons. Patients classified as ASA category IV ($n = 2$) were excluded as well as those who did not give their consent to participation ($n = 7$). Treatment protocol violations ($n = 5$) and unavailability of one of the participating anaesthesiologists ($n = 48$) were the other principle reasons for exclusion.

In group I, a 16 Fr gauge nylon epidural catheter with three lateral holes was placed at the level of thoracic 8/9 or 9/10 vertebrae and was advanced 4–5 cm into the epidural space. Before intubation, group I patients received bupivacaine 0·75 per cent. After operation they received bupivacaine 0·25 per cent continuously for 3 days. The dose was adjusted to keep the dermatomes T5–L2 blocked. Spread of analgesia was determined by the pin prick method. In cases of regression of the upper level of analgesia, additional single doses of bupivacaine

Table 1 *Pre and perioperative features of group I (TEA plus general anaesthesia) and group II (general anaesthesia alone)*

	Group I ($n = 57$)	Group II ($n = 59$)
ASA classification		
1	4	3
2	29	36
3	24	20
Preoperative morbidity		
Diabetes mellitus	4	4
Hepatopathy	8	13
Lung disease	29	31
Congestive heart failure	7	5
Hypertension	21	20
Coronary artery disease	20	16
Operations		
Rectal excision	2	3
Deep anterior resection	19	17
Anterior resection	19	27
Hartmann's procedure	1	1
Colectomy	1	1
Right hemicolectomy	8	7
Others	7	3
Surgeons		
A	24	21
B	15	15
C	9	8
D	2	4
E	3	1

ASA, American Society of Anaesthesiology

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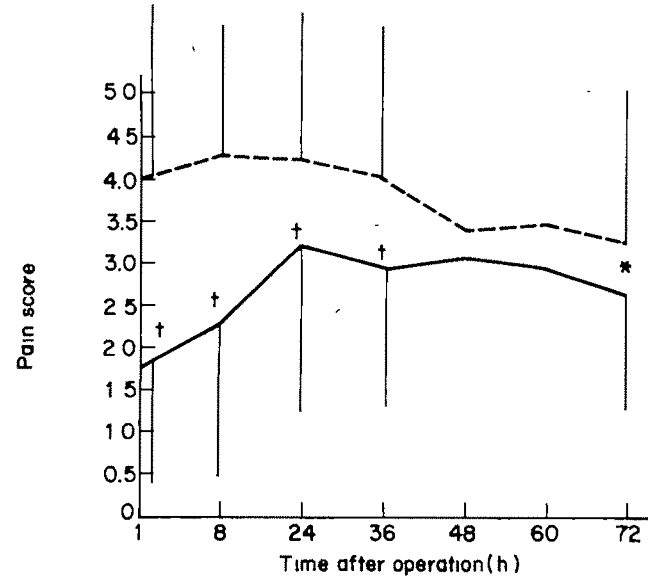


Figure 1 *Mean postoperative pain score (nominal analog scale 1–10). ——, group I, ---, group II. Standard deviation is shown where means are statistically significantly different.* $^{*}P<0{\cdot}05$, $^{\dagger}P<0{\cdot}005$

0·25 per cent were administered TEA was discontinued if complications or technical problems occurred

Both groups received general anaesthesia (fentanyl, barbiturate, vecuronium, nitrous oxide, oxygen) for intubation and placement of a central venous catheter In the epidural group anaesthesia was maintained without opioids using nitrous oxide, oxygen, bartiburate, vecuronium and bupivacaine, whereas in group II nitrous oxide, oxygen, isoflurane 0·5 per cent, fentanyl and vecuronium were given After operation patients in group II received systemic analgesics: intramuscular piritramide 7·5–15 mg, tramadol hydrochloride 50–100 mg (a less potent centrally acting opioid analgesic of the agonist type, currently under clinical development in the UK) or a simple analgesic, if requested

The following parameters were documented for comparison: pain score at registered intervals (1, 8, 24, 36, 48, 60 and 72 h after operation), body temperature (twice daily, up to 12 days), onset and frequency of defaecation up to 10 days, amount of transfused blood and blood substitutes and the frequency of blood transfusions, number of days spent in intensive care and in the hospital, and number and type of complications. Clinical monitoring was performed by three board certified anaesthesiologists

Defaecation was defined as discharge of formed or viscous faeces Body temperature was measured in the inguinal region. Only temperature elevations after the first postoperative day were registered. In the early period after surgery visual analog scales are difficult to use in some patients owing to impaired cooperation. Therefore pain was determined by using a nominal analog scale on which the patients were asked to rate verbally the level of pain they were experiencing between 1 (no pain) and 10 (unbearable pain)

Peritonitis, sepsis and anastomotic leakage were considered as life threatening complications. Abdominal wall dehiscences (without primary bacteriological contamination) and abdominal wall abscesses were documented.

Statistical methods

Student's *t* test was used to assess the significance of differences in the amounts of infused starch or protein solution and blood, the pain score, the duration of bladder catheterization, the time interval until defaecation, and the length of hospital stay after surgery.

The χ^2 test was used to analyse the incidence of defaecation, bladder catheterization, positive bacteriological cultures, days of elevated body temperature, blood transfusions, surgical complications, and the need for intensive care treatment and ventilatory support

Results

Pain score and difficulties with the analgetic regime

The pain scores were significantly lower until the end of the first postoperative day in group I (*Figure 1*).

Fourteen patients in group I required adjustment to the pain treatment regimen. Six patients showed unilateral epidural block. In four patients the epidural catheter was withdrawn involuntarily. The condition of two patients with congestive heart failure deteriorated under continuous bupivacaine but improved after the drug was discontinued. In one patient epidural analgesia spread from T2 to T11 and one catheter was placed into the subdural space. All adjustments in group I were performed after satisfactory initial pain relief.

Only one patient in group II experienced comparable difficulty with the analgesic regimen. After receiving 60 mg piritramide over 4 h during the evening of the operation day, she still suffered from pain. TEA was used which allowed nearly complete relief of pain.

The mean(s.d.) bupivacaine dose had to be increased from 19·2(4·0) mg/h on the evening of operation to 22·2(6·3) mg/h on the third postoperative day ($P<0{\cdot}05$) The mean number of blocked dermatomes in patients with epidural analgesia regressed from 8·3 on the evening of operation to 6·6 on the third postoperative day (*Figure 2*). The number of patients receiving bupivacaine decreased from 55 on the day of surgery to 34 by the third postoperative day. Up to the end of the second day after operation group II patients received significantly more frequent systemic analgesics than group I patients (*Figure 3*).

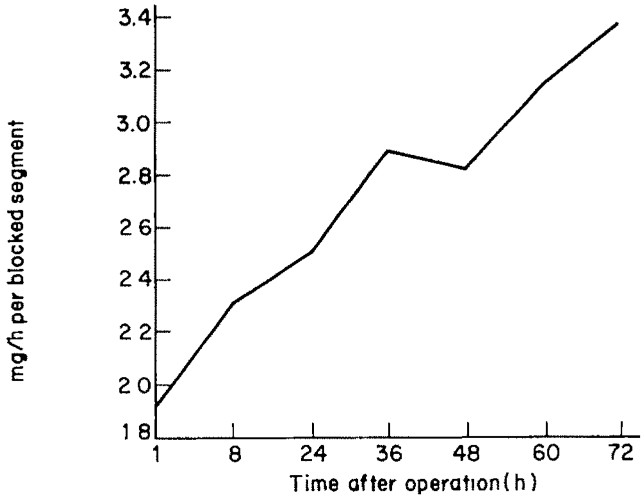


Figure 2 *Tachyphylaxis of continuous epidural bupivacaine 0·25 per cent. Data given as mg/h per blocked dermatome segment Patients without analgesic spread have been excluded*

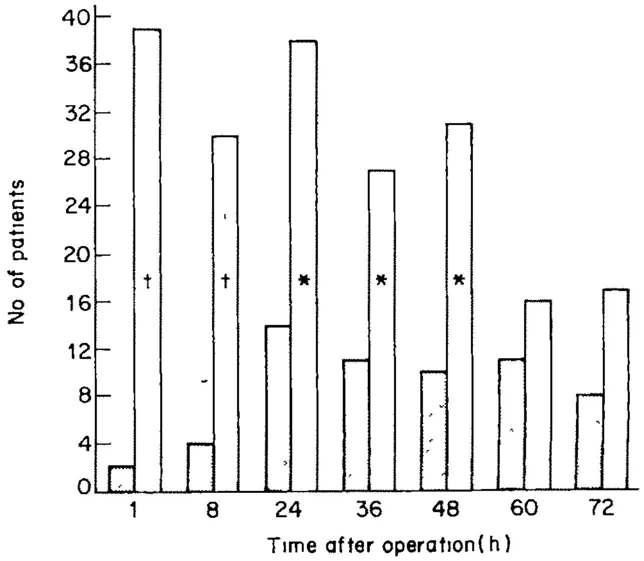


Figure 3 *Number of patients receiving systemic analgesics after operation* ▨, *group I;* ☐, *group II* $^{*}P<0{\cdot}05$, $^{\dagger}P<0{\cdot}005$

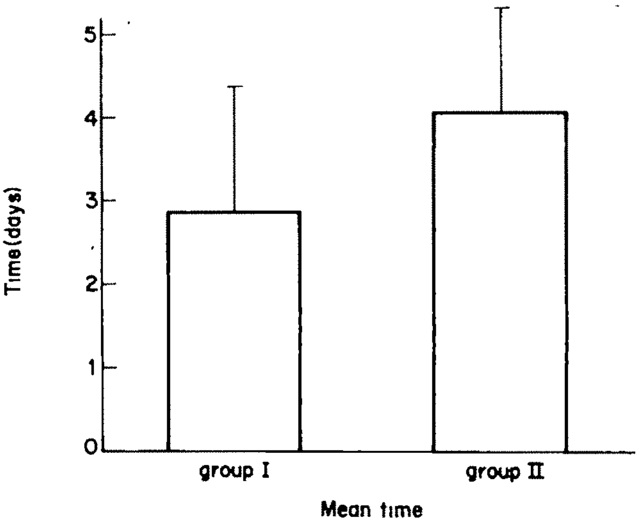
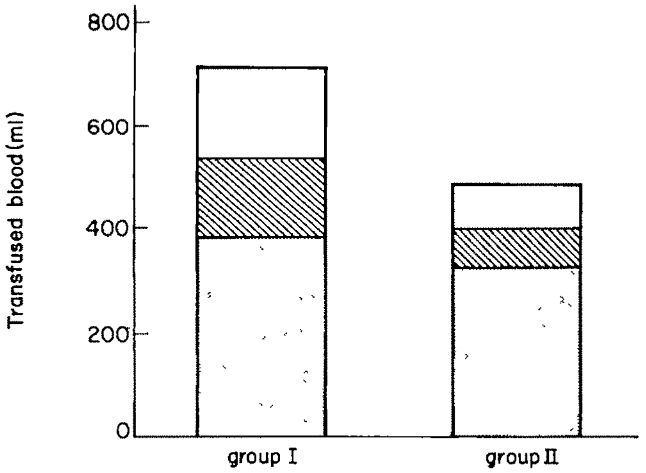


Figure 4 *Mean time and standard deviation in days until first postoperative defaecation The difference is highly significant* ($P<0{\cdot}001$)



		group I	group II
Total		713	490
Mean(s d)	□	177(446)	90(311)
	▨	154(323)	73(254)
	□	382(461)	327(439)

Figure 5 *Amount of transfused blood (ml) The differences are not significant. Numbers are mean(s.d.).* □, *during operation;* ▨, *recovery room,* □, *later*

Defaecation

Mean initial onset of defaecation is shown in *Figure 4*. By the fourth postoperative day 37 group I patients had defaecated while only 17 patients in group II had done so ($P<0{\cdot}05$). By the sixth postoperative day all but four patients in group I had defaecated compared with all but five in group II.

Blood transfusion and colloids

The amount of transfused blood is shown in *Figure 5*. The number of patients receiving blood transfusions was higher in group I taking all postoperative transfusions into account (*Table 2*). The amount of infused protein and starch solution was significantly higher in group I patients (*Table 3*).

Positive bacteriological cultures

Ten group I patients had positive bacteriological cultures taken from the field of operation compared with seven patients in group II. The number of positive cultures from urine was not significantly different between the groups.

Elevated temperature

Patients with continuous epidural analgesia more often showed elevated body temperature above 39°C, on 20 days in 11 patients in group I compared with 2 days in two patients in group II ($P<0{\cdot}05$). There was no significant difference in temperature elevations over 38°C between the groups.

Postoperative mechanical ventilation and critical care therapy

Twenty-eight patients in group I were mechanically ventilated after operation (11 for at least 1 day) compared with 26 patients in group II (ten for at least 1 day). Twenty-four hours after surgery 28 group I patients still remained on the intensive care unit compared with 17 group II patients ($P<0{\cdot}05$).

Postoperative hospital stay

The mean duration of postoperative hospital stay was not statistically different. Mean(s.d.) stay in group I was 19·9(12·7) days and in group II 18·9(18·3) days Considering only patients who did not experience life threatening complications, those with continuous TEA stayed longer in hospital. Mean(s.d.) stay in group I ($n=46$) was 16·6(7·5) days and in group II ($n=49$) 14·0(4·9) days ($P<0{\cdot}05$).

Life threatening surgical complications

Five anastomotic leaks occurred in group I, two of them resulting in peritonitis. In group II there were three leaks, one leading to peritonitis. One patient in group II developed peritonitis after ileus and another patient in this group suffered from sepsis after an abdominal wall abscess. Looking especially at patients with anterior or deep anterior resection, there were five leaks in group I patients compared to 1 in group II. Nine minor complications occurred in each group (including seven abdominal wall abscesses in group I and three in group II.

Life threatening general complications

One patient in group I had a myocardial infarction and three more had other cardiopulmonary complications. One patient suffered a stroke. In group II four complications occurred: one lethal myocardial infarction, two cardiopulmonary complications and one deep vein thrombosis

Discussion

Analgesia

The efficiency of continuous epidural analgesia for pain relief after abdominal surgery has been documented in numerous studies for different populations[1,2,4–6]. In the present study, significantly lower pain scores were registered in group I patients up to the end of the first day after operation, corroborating these previous results.

Table 2 *Number of patients receiving blood transfusions*

	Group I	Group II
Intraoperative	28	24
Recovery room	13	7
Intraoperative plus recovery room	36	27
Total	38	28*

$^*P<0{\cdot}05$

Table 3 *Mean(s d) colloid transfusion (ml), intraoperative plus recovery room*

	Group I	Group II
Protein*	394 (380)	178 (259)
Starch†	456 (272)	302 (264)
Total*	850 (451)	481 (398)

$^*P<0{\cdot}001$, $^\dagger P<0{\cdot}005$

The present study also demonstrated the development of tachyphylaxis to epidural local anaesthetics. Especially when administering continuous bupivacaine one has to increase the dosage to maintain the level of analgesia. Whether other strategies of systemic analgesia would result in pain relief comparable with the one achieved with continuous epidural analgesia was not with the scope of this study.

Bowel function

Normally no paralysis of the small intestine occurs after surgery, but transport out of the stomach and through the large intestine may be considerably delayed[7–11]. The stimulating effect of epidural analgesia on colonic peristalsis, especially if it is prolonged for 48 h, has been documented by several authors[2,3,5,12,13]. The results of this study substantiate this finding

Blood replacement

The blood saving effect of epidural anaesthesia without general anaesthesia used has been reported in orthopedic surgery[14]. Studies looking at abdominal surgery with combined regional and general anaesthesia have not shown any effect of the additional regional techniques regarding blood loss[3,6] The present results did not demonstrate any blood saving effect in group I patients. These patients showed a tendency toward a higher transfusion rate than those in group II. However blood loss was not quantified. One has to consider that these results could reflect the sympatholytic effect of epidural analgesia with bupivacaine.

Foley catheter

Most patients under continuous thoracic epidural analgesia require a Foley catheter for urinary retention Only a few patients retain bladder control. Therefore the longer dependency on Foley catheters in group I patients may be attributed to the study design.

Positive bacteriological cultures and temperature elevations

No previous study comparing patients with and without epidural analgesia was identified. The present study recorded more frequent temperature elevations above 39°C in group I patients. This may be due to the more extended catheterization of the bladder in these patients.

Postoperative mechanical ventilation

The relatively high incidence of postoperative mechanical ventilation in this study reflects a liberal use of this technique and is related to preoperative morbidity, the type and extent of surgery and intraoperative blood gas analysis. There was no difference in the frequency of postoperative mechanical ventilation between the groups.

Critical care therapy

Twenty-four hours after surgery a significantly larger number of group I patients remained on the critical care unit. This may be due to the need to monitor continuous thoracic epidural analgesia in the early postoperative period.

Hospitalization

One might expect that epidural analgesia following abdominal surgery could result in a shorter hospital stay owing to earlier defaecation and mobilization. However, several studies have demonstrated that this is not the case[6]. This study did not demonstrate any difference between the groups in length of hospital stay. However, if patients suffering life threatening complications were excluded from both groups, patients with epidural analgesia remained longer in hospital.

Mortality

There are no data to show positive effects of epidural analgesia on mortality after abdominal surgery[3,6]. In this study two out of 116 patients died. Both belonged to group II. One patient died on the third day after operation from a myocardial infarction. The other patient had an anastomotic leak and died 3 months after operation due to multiple organ failure. All four patients (two in each group) who developed peritonitis were treated with 'Etappenlavage'[15] and survived.

Anastomotic leakage

Anastomotic leakage is the most important surgical complication after colonic surgery The frequency of detectable leakage varies according to different studies from 6 to 15 per cent. The use of autosuture instruments has not reduced this figure[16–19] Prospective studies using radiopaque fluid have shown a much higher frequency (up to 51 per cent) of anastomotic leakage without clinical symptoms[17].

The incidence of leakage depends on the anatomic site of resection. Left side colonic anastomoses have a higher leak rate than right side anastomoses. Deeper anterior resections have a higher rate than less deep ones[20], and the skill of the surgeon may influence the rate of this complication[19]. Other relevant factors are prolonged intraoperative hypotension, blood volume depletion, and hypoxaemia. The use of neostigmine and banked whole blood have also been cited as causative factors[21–24].

One might expect that segmental autonomic blockade would benefit the blood supply to the anastomosis and improve its integrity[25]. Studies examining the influence of postoperative epidural analgesia on the rate of anastomotic leakage after colonic surgery are not available However, some case reports exist concerning early postoperative anastomotic leakage during epidural analgesia[3,12,26,27].

In this study the 6·9 per cent incidence of leakage is rather low. In this respect there was no significant difference between the two groups, and so the theoretical advantage of continuous thoracic epidural analgesia was not substantiated. However, the numbers of patients in each group were not sufficiently large enough to detect anything other than major improvement and small improvements may have gone unrecognized.

So far the relationship between epidural analgesia and anastomotic leakage is unknown However, it may be that the earlier onset of postoperative colonic peristalsis in patients with epidural anaesthesia uncovers leakage or promotes clinically silent leaks into clinically obvious ones. In terms of anastomotic leakage, the results of this study would not suggest the liberal application of epidural analgesia.

Abdominal wall abscess

Intraoperative bacteraemias are common during colonic surgery, and contamination of the field of operation with intestinal bacteria cannot be reliably prevented. Surgical trauma compromizes the immune response of the patient[28]. Perioperative prophylaxis with antibiotics has unquestionably reduced the risk of infection[29].

Theoretically, segmental sympathetic blockade might enhance blood flow in the wound area and so exert a positive effect on wound healing. However several authors have demonstrated that this is not the case in abdominal surgery[6,30]. Indeed, there are indications that continuously applied local anaesthetics might exert an inhibitory effect on leucocyte function[31–33]. The results of this study did not show any significant difference of the rate of infection between the two groups. Taking only abdominal abscesses into account, there was a tendency towards a higher incidence in group I.

Conclusions

This study does not suggest any significant benefit from TEA in colonic surgery, compared with a conventional systemic analgesic regimen. However, in selected patients such as those with severe pain or those prone to develop a postoperative ileus, continuous TEA may have some merit.

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Single layer anastomosis in the upper gastrointestinal tract

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A total of 466 single layer upper gastrointestinal anastomoses were made in 349 patients during an 11-year period. Six (1·3 per cent) anastomoses leaked. Radiological leakage was seen in one of 24 (4·2 per cent) oesophagogastric/jejunal anastomoses. There were no leaks after 66 gastrojejunal anastomoses; one of 84 (1·2 per cent) gastroduodenal anastomoses leaked and was converted to a gastrojejunal anastomosis. Two of 121 (1·7 per cent) biliary–enteric anastomoses leaked and both were successfully managed without reoperation. Two of 171 (1·2 per cent) enteroenteric anastomoses leaked, both in patients with established intraperitoneal sepsis which proved fatal. Of the 349 patients, 13 (3·7 per cent) died in hospital or within 30 days of operation but in only two was anastomotic leakage implicated. Single layer appositional upper gastrointestinal anastomoses are simple, safe and economic.

Keywords: Gastrointestinal anastomosis, single layer anastomosis, leakage

Anastomotic integrity is an important determinant of immediate outcome in gastrointestinal surgery and anastomotic technique is an important factor in healing. The variable and often high risk of anastomotic leakage after colorectal anastomoses is well recognized[1] and the safety of single layer anastomoses in this relatively high risk area is well known[2,3]. The outcome of single layer anastomoses in the upper gastrointestinal tract over an 11-year period is now presented.

Patients and methods

Data collection and analysis

From January 1977 to December 1987 all patients undergoing an abdominal operation under the care of one surgical team were included in a prospective audit. Information relating to diagnoses, operations and outcome was recorded on standard forms at the time of operation, on discharge and at follow-up 4–6 weeks after leaving hospital. A total of 349 patients underwent 466 anastomoses in the upper gastrointestinal tract, almost all of which were made either by a consultant or a senior registrar. All patients with oesophageal, gastric, biliary and enteric anastomoses were included; ileocolic anastomoses were excluded.

Anastomotic technique

During the 11 years anastomotic technique evolved to an appositional method using a single layer of serosubmucosal sutures at almost all sites. An interrupted technique using 3/0 braided polyamide was used for oesophagogastric, oesophagojejunal, gastroduodenal and enteroenteric anastomoses. In oesophageal anastomoses, however, in exception to serosubmucosal placement the full thickness of the oesophagus was included in the suture. During the first 7 years a closed method of enteroenteric anastomoses[4] was used in about 50 per cent of instances but this was abandoned and since 1984 all enteroenteric anastomoses were made with an open appositional serosubmucosal technique. Similarly, from 1977 to 1983 the majority of gastrojejunal anastomoses were made in two layers but since 1984 a single layer of continuous 3/0 polydioxanone or polyglyconate was used, either 'all-coats' or serosubmucosal. Biliary–enteric anastomoses were made with a single layer of continuous 3/0 or 4/0 monofilament suture (polypropylene at first, later replaced by polydioxanone or polyglyconate) taking the full thickness of the bile duct or gallbladder wall and the serosubmucosal layers of the intestine.

Anastomotic leakage

With the exception of oesophageal anastomoses, where postoperative radiological contrast studies were routine, the diagnosis of anastomotic leakage was made on clinical criteria and then investigated with radiological contrast studies. Management varied depending on the severity of peritoneal contamination.

Results

Six (1·3 per cent) of 466 single layer anastomoses leaked (*Table 1*). There was one oesophagojejunal leak detected radiologically which sealed without intervention. None of 66 gastrojejunal anastomoses leaked. There was a single leak after 84 gastroduodenal anastomoses which was managed successfully by conversion to a gastrojejunal anastomosis and closure of the duodenal stump.

Two (1·2 per cent) open enteroenteric anastomoses leaked in patients undergoing a third and fourth laparotomy for severe established intraperitoneal sepsis. One patient required a second operation for anastomotic obstruction after a closed enteroenteric anastomosis.

Two patients (1·7 per cent) developed a bile leak after biliary–enteric anastomoses; both closed spontaneously without intervention.

Table I *Single layer anastomoses in the upper gastrointestinal tract done in the period from 1977 to 1987*

	No. of anastomoses	No of leaks
Oesophagogastric/jejunal	24	1 (4·2)
Gastroduodenal		
Billroth I partial gastrectomy	66	1 (1·5)
Vagotomy and antrectomy	18	–
Overall	84	1 (1·2)
Gastrojejunal		
Billroth II partial gastrectomy	30	–
Vagotomy and gastrojejunostomy	24	–
Gastrojejunostomy alone	12	–
Overall	66	–
Enteroenteric		
End-to-end	113	2 (1·8)
End-to-side (Roux-en-Y)	58	–
Overall	171	2 (1·2)
Biliary–enteric		
Choledochoduodenostomy	63	–
Cholecyst/dochojejunostomy (Roux-en-Y)	58	2 (3·4)
Overall	121	2 (1·7)
Total	466	6 (1·3)

(Numbers in parentheses are percentages)

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Thirteen patients (3·7 per cent) died in hospital or within 30 days of operation. Anastomotic leakage was associated with death in the two patients undergoing small bowel resection in the presence of established peritoneal sepsis.

Discussion

Single layer interrupted anastomosis was introduced to Aberdeen by H. A. F. Dudley almost 30 years ago. For several years the technique was limited to gastroduodenal, small bowel and ileocolic anastomosis. Gastroduodenal anastomoses were made with a closed technique on the posterior aspect, open on the anterior and small bowel (and ileocolic) anastomosis with a closed technique using Wangensteen's clamps. These methods were illustrated and their results between 1969 and 1974 reported by Matheson and Irving[4]. For some 20 years we have used single layer anastomosis for colocolic and colorectal anastomosis. At first a closed technique was used whenever the bowel ends were sufficiently accessible for the application of Wangensteen's clamps. Otherwise the technique was open and at first inverting although by 1974 it was usually appositional as illustrated in 1976[4] and later[5]. The closed technique was seldom used after 1979 and not at all during the past 5 years in which all large bowel anastomoses have been interrupted appositional with exclusion of mucosa (serosubmucosal). The technique is safe[3], well established and economical

Anastomoses in the upper gastrointestinal tract are generally considered to be at less risk of leakage than those in the large bowel and have not been subjected to the same degree of critical appraisal. This prospective audit documents the outcome of single layer anastomoses in the upper gastrointestinal tract over an 11-year period. Single layer anastomoses were routine except for gastrojejunal anastomoses during the first 5 years.

The theoretical advantages of a single over a two layer technique are essentially those of more rapid and reliable healing because of minimal interference with vascularity and more accurate apposition of the divided bowel. These advantages are likely to be most apparent clinically in the large bowel where tissue perfusion may be tenuous. Anastomoses in the upper gastrointestinal tract are relatively privileged in terms of vascularity and probably at reduced risk of anastomotic failure for that reason.

The vascularity of the stomach however introduces a risk of bleeding from an anastomotic suture line which underlies our persistence with a conventional two layer technique (inner all-coats) for gastrojejunal anastomosis long after it had been abandoned at all other sites Since 1984, however, coincident with the introduction of monofilament suture material with delayed absorption, single layer gastrojejunal anastomosis has been routine. Obvious bleeding submucosal vessels are sealed under vision using diathermy coagulation (clamps are avoided) Since ischaemia is not a concern the single layer suture is continuous which is simpler and quicker than interrupted suturing, and as in other sites is appositional. Serosubmucosal placement has not been constant on the gastric side where the mucosa may pout and its margin has, by choice, been incorporated. This simple technique has not been associated with either leakage or haemorrhage. We continue to use a single layer of interrupted non-absorbable serosubmucosal sutures for gastroduodenal anastomosis because of apparent safety during 25 years at a site with a reputation for leakage. The anastomosis is now made open on both posterior and anterior aspects with diathermy coagulation of bleeding submucosal vessels and is appositional.

Other exceptions to a single layer interrupted serosubmucosal technique occur in oesophageal and biliary anastomoses. In oesophageal anastomosis the full thickness of the oesophagus is incorporated and in biliary–enteric anastomoses a single layer continuous monofilament suture incorporates the full thickness of the bile duct or gallbladder and the serosubmucosal layers of the intestine. A change was made from monofilament polypropylene to polydioxanone or polyglyconate when these materials became available.

There were no leaks associated with closed single layer anastomoses but postoperative obstruction at the anastomosis does occur and did so on one occasion in this series. This recognized risk together with the theoretical disadvantages of inversion of crushed bowel ends as opposed to accurate apposition led to the abandonment of this otherwise aesthetically attractive technique.

The overall leak rate in this audit was low and would have been lower still if enteroenteric anastomoses had been avoided in favour of exteriorization in the two patients with gross established intraperitoneal sepsis undergoing repeated laparotomy.

A recent study has reported the results of a continuous single layer suture technique in 66 patients undergoing upper gastrointestinal anastomoses with a 4·5 per cent leak rate[6] compared with our figure of 1·2 per cent in a comparable group of patients in which a continuous technique was confined to gastrojejunostomy and biliary–enteric anastomosis. We have reservations about using continuous suturing throughout the gastrointestinal tract since interrupted single layer serosubmucosal, appositional, anastomosis continues to be associated with a low incidence of leakage at the most hazardous sites. The interrupted technique has advantages where access is restricted since it permits accurate placement of the posterior sutures while the divided bowel ends are widely separated.

A single layer anastomosis is the method of choice throughout the gastrointestinal tract, with modification according to site, and is simple, economic and safe.

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The long-term sequelae of ileocolic anastomosis in childhood: a retrospective survey

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The long-term effects of ileocolic anastomosis in children are not known. We therefore carried out a survey of all such patients treated at our hospital between 1971 and 1985. Thirty-seven patients were identified and invited to attend for follow-up. Twenty-seven (73 per cent) were examined and included in the survey. Mean age at survey was 7·8 years (range 1·6–17·6 years) and mean duration since operation was 6·3 years. Necrotizing enterocolitis and intussusception were the commonest indications for operation. As judged by height, weight and skin fold thickness, all patients were well nourished. Seven (26 per cent) had loose stools, five had chronic folic acid deficiency and one was vitamin B_{12} *deficient. We conclude that resection of the ileocaecal region is well tolerated in childhood and does not affect growth. Loose stools are directly related to the length of ileal resection.*

Keywords: Ileocaecal resection, loose stools, perianastomotic ulceration

The long-term sequelae of ileocolic anastomosis in childhood are unknown, but there are a number of reasons for anticipating appreciable long-term morbidity[1]. The aim of this survey was to assess the long-term effects of this procedure on bowel habit, nutritional status and growth in children.

Patients and methods

The records of all patients who underwent ileocolic resection at the Children's Hospital, Birmingham, during the years 1971 to 1985, were studied. The following details were recorded: age at operation(s), sex, primary pathology requiring resection, and whether a stoma or primary anastomosis was performed. The length of bowel resected was derived from the surgeon's operation note and from the pathology report.

There were 37 patients who satisfied the criteria for inclusion in the study. Having made satisfactory progress and been discharged from surgical follow-up, they were invited by letter to attend for assessment. Twenty-six (70 per cent) responded and were examined One patient was traced to another region and was assessed and examined there by his general practitioner.

The following information was recorded. details of diet, appetite, stool frequency and consistency, and history of other illnesses, especially anaemia. Height, weight and triceps skin fold thickness were measured and compared with Tanner–Whitehouse standards[2,3] Percentages of the median weight-for-height, weight-for-age, and height-for-age were calculated using Cole's slide rule[4].

Haematological investigations comprised full blood count, estimations of serum vitamin B_{12}, folate, ferritin and red cell folate Specimens of faeces were taken on 3 separate days, after suitable dietary restriction to avoid false positives, and tested for occult blood using the Faecatwin test (Labsystems Oy, Helsinki, Finland) Colonoscopy was performed on those patients who were anaemic (haemoglobin <11 g/dl) and/or had a positive Faecatwin test.

Results

The age range at survey was 1·6–17·6 years (mean 7·8 years) and the mean time since operation was 6·3 years. *Table 1* lists the indication for operation in the 27 patients. Resection with primary end-to-end anastomosis was performed in 17 (63 per cent) patients and in the remainder anastomosis followed an initial ileostomy. The age at which ileocolic anastomosis was carried out ranged from 1 day to 9 years.

The estimated lengths of small and large bowel resected are detailed in *Table 2* All patients were taking normal diets and only two complained of poor appetite. Seven (26 per cent) patients passed loose stools more often than three times daily (*Figure 1*). This included three patients who had more than 60 per cent of their colon remaining but had more than 40 cm of ileum resected. Of the remaining four patients three had 10–40 cm of ileum resected. Only one patient had a resection of less than 10 cm. Two patients with approximately 60 per cent of their colon resected but with almost complete lengths of ileum preserved did not have loose stools (*Figure 1*). There were no significant differences between the observed values of weight-for-height and height-for-age and the normal population[2,3].

Five (19 per cent) patients were found to have a microcytic anaemia (haemoglobin 5, 8·7, 10, 10·2 and 10·3 g/dl respectively). One patient had a low serum level of vitamin B_{12} of 130 ng/l (normal range 150–1000 ng/l). Only two patients were taking vitamin B_{12} supplements prophylactically. Five patients had low levels of red cell folate with a mean value of

Table 1 *Indications for ileocolic anastomosis in 27 patients*

Indication	No of patients
Necrotizing enterocolitis	10
Intussusception	7
Colonic atresia	2
Ileal atresia	2
Ileal volvulus	2
Ileal duplication	1
Lymphoid hyperplasia	1
Appendix mass	1
Leiomyosarcoma of ileum	1

Table 2 *Extent of bowel resection in 27 patients*

Extent	No. of patients
Small bowel	
Less than 10 cm of ileum	14
Between 10 and 40 cm ileum	10
More than 40 cm of ileum	3
Colon	
To hepatic flexure (30%)	16
To sigmoid flexure (60%)	9
More than 60% of colon	2

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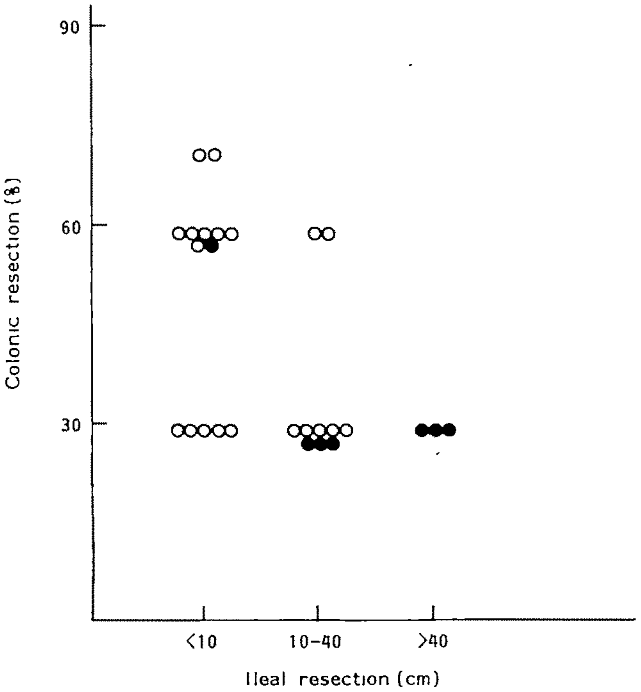

Figure 1 *Stool pattern following ileocolic resection in 27 patients* ●, *Loose stools more often than three times daily,* ○, *formed stools*

104 μg/l (normal range 120–700 μg/l). Two of these patients also had low levels of serum folate with a mean of 1·9 μg/l (normal range 3–20 μg/l). Three patients had low levels of serum ferritin with a mean of 5 ng/l (normal range 7–142 ng/l). Three patients had positive Faecatwin tests and underwent colonoscopy. Two of these were found to have ulceration in the perianastomotic region and these two had the worst anaemia. The third had non-specific proctitis.

Discussion

This survey shows that ileocaecal resection is well tolerated in children although 26 per cent will have loose stools and a small minority will develop perianastomotic ulceration[5]. In contrast to other series[1,6], resection of the right colon did not appear to cause loose stools. However, *Figure 1* shows that patients who had long segments of ileum resected were likely to develop loose stools. This may be related to several factors acting in concert: (1) loss of the ileal absorptive surface area; (2) loss of the ileocaecal valve[7]; (3) loss of the 'ileal brake' mechanism[8] and (4) loss of ileal reabsorption of bile acids[9].

Five (19 per cent) patients had low levels of red cell folate indicating chronic folate deficiency, and two of these also had low levels of serum folate indicating poor dietary intake. The low red cell folate levels in the remaining three patients who had normal serum levels cannot be explained.

In contrast to other series[10], it is noteworthy that only one patient had a low serum B_{12} level and this patient had had a minimal ileal resection. On the other hand two of the three patients with the most extensive small bowel resections were taking vitamin B_{12} prophylactically but, even if it is assumed that this was necessary, it means only three out of 27 or 11 per cent of patients had vitamin B_{12} deficiency.

Delayed ulceration that developed in the perianastomotic region[5] occurred in two patients after a latent period of many years, causing loose stools containing blood and leading to a severe iron deficiency anaemia.

In conclusion, resection of the ileocaecal region with ileocolic anastomosis will not affect childhood growth and, with prophylactic supplements of folic acid and vitamin B_{12}, will not affect nutritional status in the long term, even if large segments of small intestine and/or colon are removed. Loose stools occur in about a quarter of patients and are related to the length of ileum resected rather than the extent of colonic excision. Long-term follow-up is mandatory in these patients.

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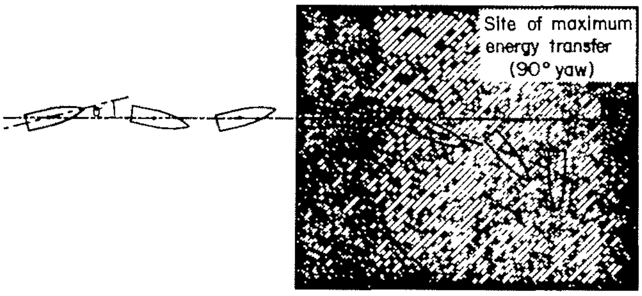

Figure 2 *The axis of a bullet during flight does not lie along its trajectory The angle (θ) between the trajectory and the axis is the angle of yaw. The spin stabilization of the bullet induces a circular motion of the nose around the trajectory. The yaw angle before interaction with the dense medium (shaded) is exaggerated in this diagram and is usually less than 1–2° in practice when the bullet has stabilized Instability due to venting of propellant gases close to the muzzle may induce high initial yaw (3–5°) at close ranges. The spin stabilization of the bullet is overcome upon entering soft tissue the yaw angle progressively increases (tumbling) and the bullet departs from the initial trajectory The retarding forces upon the bullet are at a maximum when the yaw angle is 90° The maximum energy-transfer and temporary cavity diameter are located at this point*

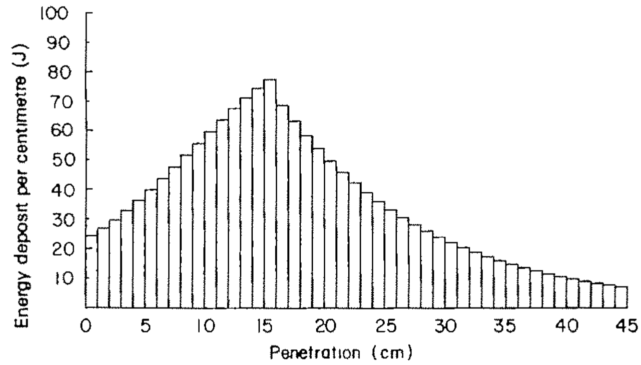

Figure 3 *The energy transfer resulting from the interaction of a high available-energy military rifle bullet with 20 per cent gelatin The energy transfer (J/cm) is plotted against penetration distance into the gelatin (cm) The bullet has tumbled (yawed) shortly after penetration; the site of 90° yaw is coincident with the site of maximum energy transfer*

as gelatin but may not be quite so obvious or significant in long wound tracks within soft tissue. The energy-transfer into gelatin for each centimetre of penetration for a military rifle bullet is shown in *Figure 3*. The site of 90° yaw is identified by the maximum degree of energy-transfer; this will also be the site of maximum temporary cavity diameter (*Figure 4*).

We have seen that high energy-transfer wounds are characterized by soft and bony tissue injury away from the path of the projectile It is tempting to presume that the temporary cavity is responsible for this injury For non-fragmenting bullets in a homogeneous elastic medium, this is the case (although stress waves associated with the penetration process may also be implicated) It must not be assumed, however, that all soft tissue involved in the formation of a temporary cavity is injured by it. This is a common misconception which has recently been the subject of criticism[2–4]; these are not theoretical arguments for they have significant implications for the degree of excision of soft tissue during primary surgery.

The formation of a temporary cavity has two consequences of significance for the majority of wounds. Firstly, it is a transient, rapid strain of tissue which may, depending on the mechanical characteristics of the tissue, produce laceration or contusion. Secondly, contaminants such as clothing taken into the wound may be widely dispersed in fascial planes and lacerated tissue by the temporary cavity

In the body as a whole, we cannot generalize about the extent of soft tissue injury occurring radial to the track as the result of the formation of a temporary cavity. In dense, homogeneous tissues, particularly if enclosed within a connective capsule or casing (liver, spleen and brain are examples), the effects of cavitation may be quite devastating; the physiological consequences of injury to these sites are rather obvious – high energy-transfer injury in these circumstances carries a very high mortality rate.

The position as far as skeletal muscle is concerned is less clear and more contentious. The rapid strain produced by the cavity produces contusion injury and, close to the track, radial laceration may be seen occasionally. The viability of contused muscle is difficult to ascertain; the judgement of the surgeon based on experience and indications such as colour, consistency, contractility and capillary bleeding has long been relied upon but is now being called into question by some authors[5,6]. They suggest that excision of skeletal muscle in peripheral wounds has been too radical and that in practice very little tissue needs to be removed[7]. There are others who maintain that most of the soft tissue involved in the temporary cavity must be excised[8,9]

An important purpose of wound excision is the removal of the source of infection. The widespread contamination, particularly in the military environment, may lead to excision of soft tissue that is contused but may be viable. This is a very contentious undertaking, for it is rarely necessary in the civilian environment and its necessity is therefore doubted by civilian surgeons. It is of note that, while military surgeons and civilian surgeons who have had war experience recognize the need for this approach, they would add that the excision of viable but contaminated tissue requires experience and value judgement The procedure is likely to be of value where infection in large numbers of casualties is produced by inappropriate excision: such a time is war.

Indirect injury by projectiles may extend to other types of tissue; for example the spinal cord may be involved in wound tracks close to the vertebral column[10,11]. The exact mechanism of this form of injury has not been fully elucidated. It has been suggested that compressive stress waves (colloquially and inaccurately called shock waves), generated in blood vessels and soft tissues by the passage of the bullet, may be involved. Some authors suggest, for example, that abdominal injury may result from high energy-transfer penetrating wounds to the thigh[12]. Although stress waves may be implicated in 'spinal shock' and indirect long bone fracture, indirect injuries produced by stress waves originating from penetrating missiles

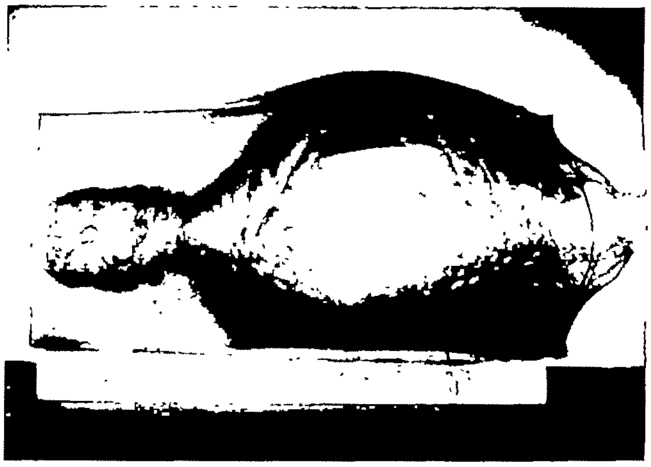

Figure 4 *The temporary cavity produced by impact of a high available-energy military rifle bullet with 20 per cent gelatin This picture was taken about 2 ms after the bullet entered the block from the left. The maximum diameter of the cavity corresponds to the site of maximum energy transfer (compare with* Figure 3) *It must not be assumed that all, or even a significant proportion, of the soft tissue affected by the temporary cavity is injured by it*

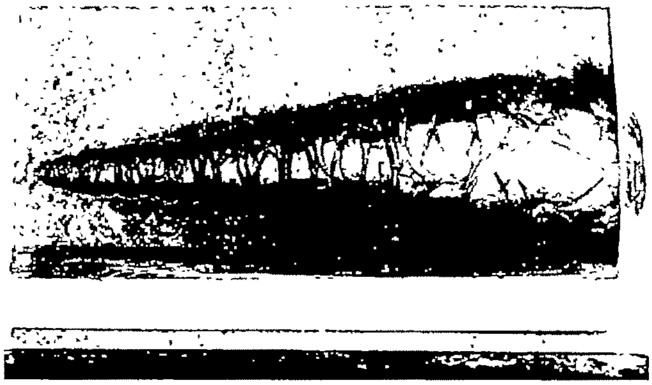

Figure 1 *Impact of a high available-energy projectile upon the ballistic simulant, 20 per cent gelatin. The projectile was broadly cylindrical in shape and did not result in significant change in presented area during the penetration process The projectile entered the block from the right and has resulted in the formation of a temporary cavity, the maximum diameter of which is close to the entry site where retardation forces are at a maximum. The cavity will eventually collapse and, within the body, may result in injury to tissues peripheral to the track. The incidence of these indirect injuries is determined by the mechanical properties of the tissues penetrated*

contaminated with foreign bodies such as clothing, skin and soil.

Antipersonnel fragments capable of penetrating skin have a range of impact velocities from about 100 m/s to beyond 1000 m/s but in spite of these very high velocities they generally result in wounds with the soft tissue injury principally confined to the immediate track of the missile.

Bullets have greater range and penetrating power and are often classified as 'low velocity' or 'high velocity'. The classification arises from the nature of the weapon firing the projectile: low velocity projectiles are generally propelled from hand guns and high velocity bullets are fired from rifles. As with all generalizations, this may be true for most cases but there are notable exceptions. The major criticism of this type of classification is that it is often implied that low and high velocity projectiles equate to two specific wound classifications of the same name, thus implying that high velocity projectiles are always associated with severe injury. This is not the case and the impact velocity of a projectile can be a misleading indicator of its potential for injury and should not be used to classify wounds or threats from weapons.

All projectiles perform work on the body, lacerating, contusing and displacing tissues. The capacity of a projectile to perform work is defined by its available kinetic energy ($\frac{1}{2}mv^2$; units are joules (J) when m is in kilograms and v is in metres per second). The available kinetic energy defines only its capacity to perform work on tissue; the proportion of this energy that is ultimately transferred at each centimetre along the track is determined by the degree of retardation of the projectile by the tissues. This in turn is governed by many factors, principally the mechanical properties of the tissue, the velocity and the presented area of the projectile as it penetrates the tissues. The available kinetic energy is 1500–3000 J for military rifle bullets. Most bullets from hand guns have available energies of about 300–500 J. Antipersonnel fragments have low available energies and, in those casualties surviving to reach surgery, available energies would have ranged from about 10 to 150 J.

An appropriate classification of the work performed within a wound is the 'energy-transfer'. It is important to differentiate at this stage between mechanical distortion (work) that arises from the energy-transfer and the pathophysiological consequences of this distortion. Some elastic tissues may have significant work performed on them but modest tissue injury results (see below). Further, it is important to realize that projectiles may produce indirect injury to tissues not directly in their path. A general classification of the extent of soft and bony tissue involvement is based upon the incidence of indirect injury.

In low energy-transfer wounds, soft tissue injury is confined to the track of the projectile The wounds arise simply from the cutting action of the projectile as it penetrates the tissues. Most antipersonnel fragments and many hand gun bullets produce wounds of this classification.

In high energy-transfer wounds, injury usually occurs radial to the track of the projectile in addition to the mechanical disruption (laceration and crushing) directly produced. The indirect injury peripheral to the track is produced principally by the formation of a temporary cavity (with non-fragmenting projectiles), a consequence of increasing levels of energy transferred

Temporary cavitation

If the available energy is substantially increased by using a projectile of a greater mass and velocity, not only is the penetration distance increased but, as a result of greater retardation forces leading to a greater transfer of energy, a temporary cavity is formed behind the projectile (*Figure 1*). The cavity results from the acceleration of material radial to the path of the projectile and reaches its maximum volume within 2–3 ms. The cavity pulsates and eventually collapses in elastic media such as gelatin or soft tissue.

A common misconception is that the formation of a temporary cavity is an 'all or none' phenomenon. The maximum size of the temporary cavity is related to the energy-transfer and even low energy-transfer projectiles will produce cavities, although these are quite small and may be of little biological significance: a pebble entering water at very low velocity will produce a temporary cavity whose collapse produces the characteristic 'plop'.

In a material such as gelatin or soft tissue, the size of the temporary cavity at a particular location along the wound track is determined by the energy deposited at that site. Fragments have little change in presented area as they tumble during the penetration process. The maximum energy-transfer, and hence the maximum cavity size, is close to the entry point where the velocity and thus the retarding forces are at a maximum. The formation of the temporary cavity is an important, but not the sole, feature involved in the production of high energy-transfer wounds, break-up or fragmentation of projectiles and bone may also occur, resulting in direct mechanical injury.

Yaw and changes in presented area

Most bullets are long and thin and are spun along their long axis to provide stability, and thus accuracy. The spin stabilization is overcome upon entering dense material such as soft tissue Bullets become unstable and will tumble (yaw) during their passage through the material (*Figure 2*). If the wound track is long enough, they may turn through 180° The major consequence of this yawing is that it increases the presented area of the projectile to result in significantly higher retarding forces, rather like the increased retardation experienced in dragging a flat palm of the hand through water. High retardation forces reduce further the velocity of the projectile, resulting in greater energy-transfer to the tissue. These forces are highest when the bullet is at 90° to its trajectory

The energy-transfer from military bullets may be substantial and may result in large temporary cavities. Because the bullet reaches 90° some distance into the track, the maximum size of the temporary cavity with most non-fragmenting bullets is deep within the track and not necessarily close to the entry point. If the wound track is long enough, all bullets will yaw. The feature that may differentiate the performance of bullets is the penetration distance before the yaw cycle commences. Small calibre bullets (5·56 mm) generally start their yaw cycle earlier than large calibre bullets (7·62 mm). This difference may be readily demonstrated in a clear, homogeneous material such

Surgical workshop

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Ileostomy revision with a GIA® stapler under intravenous sedation

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Ileostomy retraction is common, with an incidence ranging from 7–16 per cent[1]. Conventional management involves a local refashioning procedure after complete circumstomal mobilization or construction of a new stoma site after laparotomy[2]. Both techniques require general anaesthetic and may fail in 20 per cent of cases[3]. We describe a simple method of ileostomy stabilization using a GIA® stapling device *without* the blade (US Surgical Corporation, Norwalk, Connecticut, USA), which is suitable for both loop ileostomy or 'Brooke' end ileostomy.

Surgical techniques

The retracted ileostomy is grasped from within the lumen using three pairs of Babcock's forceps and everted to a length of approximately 4 cm. The forceps are then held by an assistant while the operator inserts a well lubricated GIA stapler *without* the blade into the lumen of the everted stoma to the level of the mucocutaneous junction (*Figure 1*) The stapler is then 'fired', placing a vertical row of staples along the length of the bowel wall Two further rows of staples are placed at 120° intervals around the stoma circumference (*Figure 2*). The Babcock forceps are then removed and the stoma maintains its everted position. Initially the stoma is unsightly but after 6 weeks the staples have 'disappeared' and the stoma appears normal

Closure of the ileostomy after the stapling procedure requires resection of the spout and an end-to-end anastomosis, but this is a safe and commonly used method[4] This closure technique might be contraindicated in patients with the 'short-gut' syndrome, diffuse small bowel Crohn's disease and in patients with an ileoanal anastomosis; hence 'stapling' revision ileostomy should probably be avoided in these groups if later closure is anticipated.

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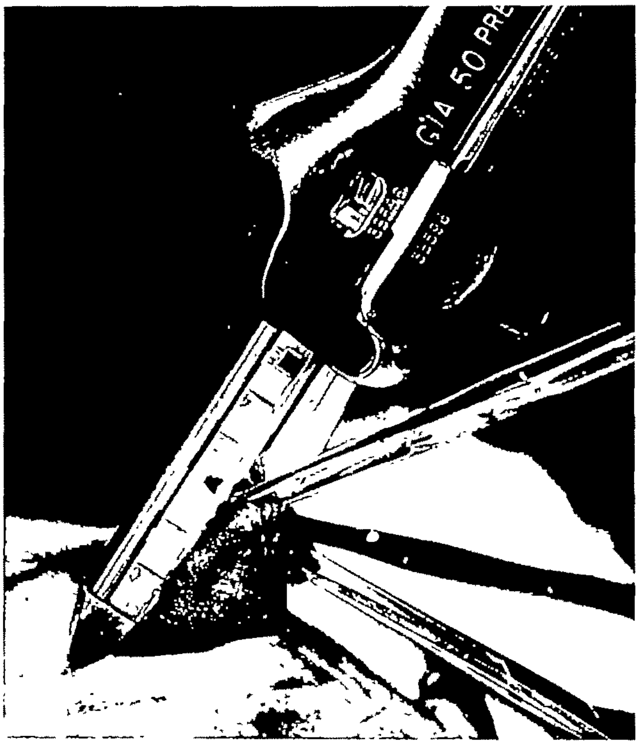

Figure 1 *The retracted ileostomy is everted and the GIA® stapler without the blade is inserted*

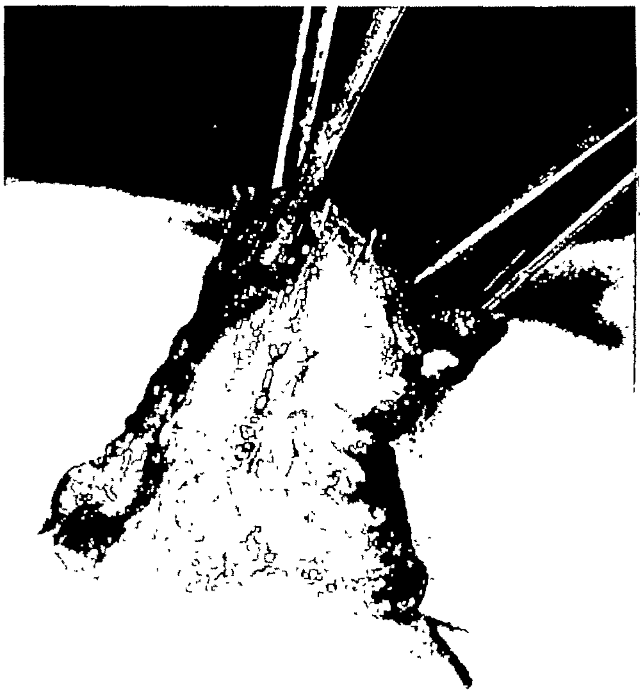

Figure 2 *Three rows of staples are inserted around the stoma to maintain its everted position*

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Prediction of the delayed complications of intestinal and mesenteric injuries following experimental blunt abdominal trauma

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Injuries to the intestine and mesentery are often found in patients undergoing laparotomy for blunt abdominal trauma. Although treatment of perforations is relatively straightforward, the same is not true for contusions. Few guidelines exist at present to aid the surgeon in deciding which injuries require resection in order to avoid the complications of delayed perforation and late stricture formation. The natural history of these non-perforating intestinal and mesenteric injuries has been examined in an experimental model to identify possible criteria on which future management can be based. In the immediate postinjury period peristalsis and local mesenteric pulsation were absent in the majority of injuries which went on to full recovery and these observations are thus of little predictive value in predicting outcome. The initial size of contusion (length of contusion along longitudinal axis of bowel) relative to bowel wall circumference (BWC) was related to complications as follows: contusion $<$*BWC* (n=*47*) – *one complication; contusion* $>$*BWC* (n=*8*) – *three complications* (P=*0·02*). *Similarly, six mesenteric injuries which produced an initial ischaemia (assessed by fluorescein) less than twice the BWC did not result in any complications, compared with four complications which occurred in ten cases when the initial ischaemia was greater than twice the BWC. These results go some way towards providing a better understanding of these injuries and in turn may help the emergency surgeon in deciding which injuries require resection.*

Keywords: Trauma, intestine, mesentery

Injuries to the intestine and mesentery are well recognized sequelae of blunt abdominal trauma (BAT)[1–4] and occur in approximately one-quarter of patients undergoing surgery for BAT[5], making the intestine the third most common organ injured after the spleen and liver[6]. Excluding mesenteric and serosal injuries, approximately 6 per cent of patients undergoing surgery for BAT have intestinal perforations[7]. Although the surgical management of intestinal perforations is straightforward, the treatment of contusions can pose a dilemma to the emergency surgeon who must decide whether they should be resected to prevent the well documented complications of delayed perforation[8–10] and late stricture formation[11–17]. This decision must be taken in the knowledge that time is poorly spent on unnecessary resections when other injuries are pressing, or in major disaster surgery when there may be a long queue of casualties awaiting their turn in the operating room.

General guidelines, taken from a wide experience of trauma surgery, are based on the principles of preserving as much bowel as possible while performing resection or repair of the injured segments[18]. Small bowel perforations and lacerations can be managed either by resection or repair[19], and it has been suggested that contusions may be treated in a similar manner, with those >1 cm in diameter requiring resection and those <1 cm needing only repair by oversewing. Operative assessment of contusions, including size of injury, presence of bleeding, absence of peristalsis and colour of bowel, is claimed to be reasonably accurate in experienced hands[20]. In the management of mesenteric injuries Rodkey and Welch consider that any disruptions affecting more than 2·5 cm of bowel should be resected and that all mesenteric haematomas should be opened, explored and haemostasis achieved[21]. These recommendations do not differ greatly from those given by Gordon-Taylor on the outbreak of World War II, based on the enormous experience gained between 1915 and 1918[22]

Despite all this, little is known about the natural history of non-perforating injuries upon which rational surgical guidelines can be based. This experimental study examines the natural history of these lesions and the predictive criteria for delayed complications.

Materials and methods

Experimental model

All injuries were produced in male New Zealand white rabbits between 2·5 and 3 kg in weight. Under intravenous pentabarbitone anaesthesia a midline laparotomy incision was made and the terminal ileum delivered into the wound. All experiments were performed under the conditions laid down by the Animal Procedures Act (1986) Because approximately three-quarters of all intestinal perforations from BAT involve the small intestine[3], the study was limited to small bowel contusions

Intestinal contusion The method of bowel injury has been previously described[23] It allows standard non-perforating intestinal contusions to be produced which are comparable to those seen in man following BAT A length of terminal ileum is placed on a cork block beneath a perspex tube from which a weight is dropped onto the exposed bowel from standard heights Force of impact can be measured in Newtons (N) and can be altered by changing both the weight and the height. In this study the force of impact ranged from 44 N to 55 N

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Table 1 *Fluorescein size of injury and late complications*

No. of perforations at 3 days		No. of strictures at 3 weeks	
>30 mm* ($n=4$)	<28 mm* ($n=23$)	>30 mm* ($n=4$)	<28 mm* ($n=24$)
1	1	2	0

* Injury size

Mesenteric injury. Mesenteric injuries were produced in the terminal ileum by ligating the marginal artery and the appropriate mesenteric arcade to produce a potential length of ischaemic bowel of 80–100 mm. This injury simulated both direct mesenteric injury (without the haemorrhage) and mesenteric detachment from the gut Measurements of size of injury were taken along the longitudinal axis of the bowel wall After initial measurements, the injured bowel was returned to the peritoneal cavity which was mass closed with a single layer of continuous 3/0 nylon suture. At the second procedure a further anaesthetic was given and the previous injuries assessed again before killing

Study 1

Three injuries were produced at intervals of 10–15 cm in each of 25 rabbits using a force of 44 N. Five animals were then killed at each of the following intervals: immediately (10 min), 24 h, 3 days, 3 weeks and 7 weeks Before killing, a second anaesthetic was given and repeat measurements taken These were macroscopic (presence of perforation/stricture, length of injury and presence or absence of mesenteric pulsation and/or peristalsis) and microscopic (fluorescein angiography) The injuries were then excised and submitted for histological examination. Measurements of mesenteric pulsation and peristalsis were not made in those five animals sacrified at 10 min.

Study 2

In a further 12 rabbits the marginal artery was ligated immediately adjacent to the area of intended injury and the contusion was then produced using 44 N The aim of this was to simulate mesenteric disruption combined with contusion Six rabbits were killed at 3 days and six at 3 weeks.

Study 3

Following the results from study 1, further injuries were produced using a greater force (51 or 55 N) and observations were taken at 3 days and 3 weeks These two time intervals were based on the histological results from study 1 By 3 days maximum tissue damage had occurred, and by 3 weeks almost complete recovery had ensued. The only observations made at these times were lesion size, as assessed by fluorescein angiography, and presence or absence of perforation or stricture formation Only one injury was made in each of 15 animals (12 with 51 N and three with 55 N). Killing of six was planned after 3 days and of nine after 3 weeks. Injuries using 51 N or 55 N were used to produce a variety of lesions. Forces in excess of 55 N produced injuries that were too severe for further study and were therefore not included.

Study 4

Mesenteric injuries, as described above, were produced in 16 animals The actual initial length of ischaemia was measured using fluorescein angiography and ten animals were killed at 7 days and six at 4 weeks Again the specimens were examined for evidence of perforation or stricture formation both macroscopically and histologically

Fluorescein angiography

A technique similar to that described by Marzella *et al.*[24] was used to assess the extent of injury. A 5 ml solution of fluorescein in isotonic saline was infused into an ear vein of the rabbit 2 min before examination Activation of the fluorescein using a Wood's ultraviolet light allowed measurements to be taken of the extent of the injury, as represented by absence of fluorescein uptake.

Histological technique

Tissue blocks of rabbit intestine were fixed in formal saline before being embedded in paraffin wax. Sections of 4 μm thickness were then cut and stained with haematoxylin and eosin.

Definitions and statistics

Perforations were assessed by finger clamping on either side and increasing the intraluminal pressure while observing for leakage of bowel contents Following resection, suspected perforations were examined histologically to confirm transmural necrosis and disruption

Strictures were defined as macroscopically narrowed areas of bowel, associated with proximal distension and fibrotic replacement of the muscularis externa on histological examination

Comparison of complication rate with size of injury and outcome was carried out using Fisher's exact test

Results

Study 1

No animals died during the observation period of the initial standard contusion study (force of injury 44 N). Peristalsis was absent in 51 out of 60 injuries at 10 min and in seven out of 15 injuries at 24 h Peristalsis was present in all 45 remaining injuries· 15 at 3 days, 15 at 3 weeks and 15 at 7 weeks. Mesenteric pulsation was absent in 12 out of 60 injuries at 10 min, in one out of 15 at 24 h, and in four out of 15 at 3 days. Mesenteric pulsation was present in all 15 injuries at 3 weeks and 7 weeks respectively. There was no observed increase in the extent of injury over the first 3 days after the initial measurement had been taken at 10 min. No correlation was found between histological evidence of mesenteric vessel thrombosis and absent pulsation.

There was only one complication, a delayed perforation which occurred at 3 days. There were no late strictures. For the reasons explained above, the perforation and stricture results at 3 days and 3 weeks were combined with those from studies 2 and 3 for further analysis.

Study 2

There was only one complication, a delayed perforation at 3 days. The incidence of complications after standard contusion with and without study 1-associated mesenteric ligation was similar, i.e one in 12 and one in 30, respectively

Study 3

There were two postoperative deaths within the observation period in this group but neither was directly related to bowel injury as there was no evidence of perforation or haemorrhage at necropsy There were no delayed perforations in the remaining 13 animals at 3 days. There were two late strictures in seven animals at 3 weeks.

Combining the injuries from studies 1 ($n=30$), 2 ($n=12$) and 3 ($n=13$) gave a total of 55 contusions in 35 rabbits for study Twenty-seven injuries were examined at 3 days and 28 at 3 weeks. There were two delayed perforations (at 3 days) and two late strictures (at 3 weeks). The relative size of injury as assessed by fluorescein is compared to the incidence of complications in *Table 1*.

The incidence of complications was related to contusion size (*Table 2*). Only one out of 47 contusions <28 mm developed complications, while three out of eight >30 mm developed complications ($P=0·02$) If a smaller contusion size was used to define the groups the difference between them was no longer statistically significant (*Table 2*). The difference in incidence of

Table 2 *Serial comparison of lesion size with the development of complications (perforation or stricture)*

Lesion size (mm)	No at risk	No of complications	Fisher's exact test
>30	8	3	$P=0·02$
<28	47	1	
>28	16	3	$P=0·14$
<26	39	1	
>26	26	4	$P=0·09$
<24	29	0	

perforation between the two groups was not statistically significant but the differing incidence in delayed strictures does reach statistical significance, zero out of 47 for <28 mm contusions *versus* two out of eight for >30 mm contusions ($P=0{\cdot}04$).

Study 4

In none of the six injuries where the actual ischaemic length (measured with fluorescein) was <45 mm were there any complications; however, four out of ten injuries where the initial actual ischaemic length was >55 mm developed complications, two delayed perforations at 1 week and two late strictures at 4 weeks.

Fluorescein angiography

Although fluorescein was an easy marker to use for assessing the extent of injury in the contusions, it was no more accurate than the naked eye. This was not the case, however, in mesenteric disruption, where fluorescein identified ischaemia which was not visible to the naked eye. The reason for this discrepancy is that contusions produced gross macroscopic changes such as subserosal haematoma and surrounding tissue injury, whereas mesenteric ligation did not

Discussion

By far the most common cause of BAT in the Western world in peacetime is road traffic accidents[6]. Figures from the Department of Transport for 1986[25] demonstrate that in Britain road traffic has increased by nearly 4 million vehicles in the last 10 years. In Scotland from 1980 to 1983 between 2 and 3 per cent of all road traffic accident victims sustained abdominal injuries. In 1986 there were 21 700 000 motor vehicles licensed in Britain and 321 000 accident victims, of whom 69 000 were considered to be severely injuried (detained in hospital or requiring treatment for fractures and major lacerations). Thus an estimated 2000 patients required medical treatment for abdominal injuries. If we assume that this represents at least 75 per cent of all cases of BAT[6,26], the estimated number of BAT patients presenting to emergency departments in Britain at present is about 2700 per year.

Performance in trauma management in the UK is currently under critical review[27] and a greater knowledge of the potential problems surrounding these intestinal injuries would be beneficial. Recent experience of air crashes and other major disasters shows that abdominal injuries are not uncommon and following any major accident a large number of casualties may set difficult priorities

Non-perforated intestinal contusions are well recognized complications of abdominal trauma[28] and, although they can occur in penetrating trauma[29], they more commonly follow BAT[4,5] They are probably commoner than is generally appreciated[30]. Injuries, primarily to the small bowel, are found in up to one-quarter of patients undergoing surgery for BAT[5], and this incidence appears to be on the increase following the more widespread use of seat belts[31,32]. Undetected perforation and the associated delay in treatment still remain the most important causes of morbidity and mortality from small bowel injury today[4,33]. Some may only be discovered at autopsy[34].

The possibility of delayed perforation following intestinal injury is well recognized[8–10]. Some authors have suggested that this results from ischaemic necrosis[10], either following transmural injury of the bowel wall or injuries to the adjacent mesentery. Our results would certainly support this hypothesis.

Poland[35] reported the first case of late stricture formation following intestinal injury from BAT in 1858 and since then many have confirmed his observations of these lesions[11–17], which occasionally result in intestinal obstruction several months later[36,37] It is well known that disruption of the blood supply to the bowel leads to gangrene, perforation and delayed stricture formation[38,39] and in the majority of these cases there is evidence of mesenteric injury suggesting that ischaemia is the prime cause[13–17,36,37]. However Marks suggested that delayed stricture could follow contusion from direct crushing of the gut against the vertebral column[40]. Observations from study 4 support the view that ischaemia is one of the causes of delayed complications which are found after BAT. It is not surprising that the incidence of complications in study 3 was related to the initial length of intestinal ischaemia and only mesenteric injuries which produced an initial bowel ischaemia of >55 mm went on to develop complications

The most striking feature of our longitudinal studies of intestinal injury is the reparative property of the rabbit small bowel which, even in the presence of extensive transmural haemorrhage, recovered in the majority of instances with barely a sign to indicate the previous trauma. In many instances conventional surgical operative assessment would have suggested resection to be the most prudent course of action which would have resulted in many unnecessary resections. Overall there were 55 contusions of which only four developed delayed complications. It is perhaps surprising that ligation of the mesentery adjacent to the contusion did not affect the natural history of the contusions, probably because the length of potential ischaemia did not reach a critical level, as defined by study 4.

Intraoperative aids used to assess the viability of intestinal injuries are based on the detection of perfusion deficits. Initially intra-arterial injection of trypan blue dye was used[41] and later refined by replacement with fluorescein[42]. The latter is more accurate in the detection of intestinal viability than either clinical judgement alone or combined with Doppler ultrasonography[43]. The ability to detect the thickness of bowel injury using fluorescein is considered to be of predictive value in the assessment of the viability after intestinal contusion[44] but whether these areas of decreased perfusion will go on to perforate or stricture cannot be assessed. Although mesenteric ischaemia results in relatively early cell changes when examined under scanning electron microscopy[45], temporarily damaged and ischaemic bowel may recover[46].

It is always difficult to extrapolate animal data to man However, the histological appearances of the small bowel are similar in rabbits and man and there is no reason to assume they would respond differently. The present results may be more usefully interpreted if the lesion size (length along bowel) is compared with the circumference of the rabbit bowel which is almost universally 28 mm in the distal ileum. Delayed complications following both intestinal and mesenteric injury may be predicted from the lesion size/bowel circumference ratio, with a low likelihood of complication when the length of contusion is less than the bowel circumference or when mesenteric injury results in an ischaemic length less than twice the bowel cirumference. Although surgeons will rarely, if ever, operate on a patient immediately after intestinal injury, the results from study 1 confirm that the size of injury does not increase during the first 3 days. These guidelines therefore hold good for contusions within this time period.

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Selective conservative management of abdominal gunshot wounds: a prospective study

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A prospective study of 111 patients with low velocity gunshot wounds of the abdomen was conducted to determine whether a policy of selective conservative management based on repeated physical examination is a safe form of treatment. Laparotomy was undertaken in 89 patients (80 per cent), seven of which were negative. Of the patients 22 (20 per cent), eight of whom were considered to have peritoneal penetration, underwent conservative management. None required delayed laparotomy. Eight patients (7 per cent) died, all deaths occurring in the positive laparotomy group. The incidence of significant intra-abdominal injury if the peritoneal cavity had been penetrated was 89 per cent. Selective conservative management may be applied safely to a limited group of patients with gunshot wounds of the abdomen.

Keywords: Abdominal gunshot wounds, selective conservative management

Negative laparotomy carries a morbidity rate of between 4·9 and 35 per cent[1–6] and a mortality rate of up to 6·3 per cent[7] Consequently, many centres adopt a selective approach in the management of patients with abdominal stab wounds, a policy proposed initially by Shaftan in 1960[8]. This approach, based on clinical examination, has undergone repeated reappraisal and has been shown to be a safe and reliable form of patient management[4–6,9–14]. An extension of this conservative policy has been applied with good effect to patients with omental protrusion, isolated hepatic injuries, and even disembowelment[15–18], but the limits of conservatism appear to have been reached

Despite this swing toward conservative management in patients with stab wounds, those with gunshot wounds of the abdomen are managed, in the main, by a policy of mandatory laparotomy[1,18–24]. This approach is based on experience in military conflicts and has been applied directly to the civilian environment However, the majority of wartime injuries result from high velocity weapons, an uncommon situation in civilian injuries where most gunshot wounds arise from low-velocity handguns.

As a result of this discrepancy a prospective study was undertaken at this institution to ascertain whether a selective policy, as employed for patients with abdominal stab wounds, should be applied to those with low-velocity gunshot wounds.

Patients and methods

During the 6-month period July–December 1988, 111 patients with abdominal gunshot wounds were admitted to King Edward VIII Hospital, Durban There were 104 males and 7 females with an age range of 12–70 years (median 24 years) The time between injury and arrival at hospital ranged from 30 min to 23 h (median 4 h) The surface anatomical definition of the 'abdomen' was from nipple line to pubis anteriorly and from inferior scapular angle to lower buttock crease posteriorly. However, because intra-abdominal inury may occur with entrance wounds outside these boundaries, radiological assessment of all patients was undertaken where feasible and those with evidence of radio-opaque missiles within the defined boundaries were included in the study regardless of the site of entrance wound. Five patients with radiological evidence of missiles within the peritoneal cavity had entrance wounds outside the surface anatomical boundaries of the abdomen Twenty-two patients had more than one gunshot wound

The decision to perform laparotomy was based on physical examination and radiological assessment. Shock, generalized peritonitis, leakage of intestinal content through the wound, haematemesis, proctorrhagia, and frank haematuria with an infraumbilical entrance wound indicating bladder trauma were all indications for abdominal exploration Through and through gunshot wounds of the abdomen were not absolute indications for surgery. Those patients with tenderness confined to the wound or wound track and without evidence of cardiovascular instability underwent serial examination and assessment at two-hourly intervals

All patients had chest and abdominal radiographs unless immediate laparotomy was deemed necessary for intractable hypotension. Radiological indications for operative intervention were the presence of free intraperitoneal gas, and radio-opaque missiles within the peritoneal cavity associated with supradiaphragmatic entrance wounds, the latter indicating diaphragmatic injury. The presence of a missile within the peritoneal cavity associated with an infradiaphragmatic entrance wound and an absence of physical signs was an indication for observation Renal angiography was performed on those patients with frank haematuria and suspected renal injury. Embolization was the treatment of choice where appropriate

A positive laparotomy was defined as one in which repair or drainage of a damaged viscus was required to prevent complications A laparotomy was considered negative if there was no peritoneal penetration, penetration without visceral injury, or visceral injury not requiring repair or drainage.

Results

Of the 111 patients, 89 (80 per cent) underwent laparotomy and 22 (20 per cent) were observed (*Table 1*).

Laparotomy group (n = *89*)

The median time from injury to arrival at hospital was 4 h. Using the above criteria 82 patients (92 per cent) had a positive laparotomy and seven (8 per cent) underwent unnecessary operation. Of these seven patients, two had peritoneal penetration without significant injury. In the remaining five patients, the missile had failed to enter the peritoneal cavity. Entrance wounds only were found in 45 patients in the positive laparotomy group and 14 of these were multiple. Six patients in the negative laparotomy group had entrance wounds only, all of which were single. Through and through injuries occurred in 37 patients in the positive laparotomy group and in one patient in the negative laparotomy group

The decision to perform laparotomy was based on the clinical finding of obvious peritonitis in 67 patients, shock in 17 patients, delayed onset of peritonitis in three patients and

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Table 1 *Clinical findings in 111 patients with abdominal gunshot wounds*

	Positive laparotomy ($n=82$)	Negative laparotomy ($n=7$)	Observed ($n=22$)
Peritoneal penetration	82	2	8
No peritoneal penetration	0	5	14
Entrance wound only	45	6	12
Entrance and exit wounds	37	1	10
Multiple wounds	14	0	0
Indications for laparotomy			
Clinical	80	7	–
Radiological	2	0	–
Mortality	8	0	0

Table 2 *Organs injured* versus *mortality rate*

No. of organs injured	No. of patients	Deaths	Mortality rate (%)
1	11	1	9
2	33	1	3
3	21	2	10
4	12	2	17
5	4	1	25
>5	1	1	100

radiological evidence of free intraperitoneal gas in two patients, one of whom was paraplegic from a coexistent spinal injury. All patients who had a negative laparotomy exhibited signs of spreading abdominal tenderness The decision to operate was made, therefore, on purely clinical grounds in 98 per cent and was made on initial evaluation in 97 per cent of patients.

There were a total of 214 organ system injuries, the majority being in the small intestine (56 per cent), colon (53 per cent), stomach (28 per cent), liver (27 per cent), and diaphragm (18 per cent). The vast majority of patients suffered two or more organ injuries (*Table 2*) and, with the exception of one patient who died with a single organ injury, the mortality rate was proportional to the number of organs injured. Eight patients (9 per cent) in the laparotomy group died, half of whom were in profound shock on admission and all of whom had positive findings at laparotomy. The hospital stay of survivors ranged from 5 to 160 (median 10·5) days in the positive laparotomy group and from 3 to 10 (median 6) days in the negative laparotomy group.

Observed group (n = 22)

The median time from injury to arrival at hospital was 4 h. Twelve patients had sustained entrance wounds only and ten had both entrance and exit wounds. All had been injured with a single bullet. Using a combination of anatomical assessment of the likely path of the bullet in those with through and through wounds, and radiological assessment of those with entrance wounds only, penetration of the peritoneal cavity was either strongly suspected or confirmed in eight patients. In three of these radiography showed the bullet in the liver area and in four patients, with through and through injuries of the right hypochrondium, the bullet track was assumed to have involved the liver. In the remaining patient the bullet had entered the mid-abdomen to the left of the umbilicus and exited via the left lumbar area. This patient presented 23 h after injury with a soft abdomen and was therefore observed Using the same approach penetration was thought unlikely in the remaining 14 patients. Tangential wounds were confirmed in four patients by the passage of a Foley catheter along the entire length of the wound track. Clinical assessment, repeated by the same examiner where feasible, showed resolution of all abnormal findings within 12 h of admission.

No patient required delayed laparotomy and there were no deaths in this group. No immediate complications were incurred from failure to debride the wound track or from retained missiles, despite possible contamination from foreign bodies. Although long-term follow-up is notoriously poor in this environment, self-referral is common if complications arise following discharge from hospital; however no patient required re-admission following conservative treatment. Hospital stay ranged from 1 to 196 (median 3·5) days, prolonged admission being required for spinal injuries in two patients.

Discussion

Trauma and interpersonal violence are escalating in many countries[20,24], a situation referred to recently as the neglected epidemic[25]. In South Africa the problem is widespread throughout all ethnic groups and is increasing almost exponentially[24]. In Natal, at this institution, the incidence of gunshot wounds to the abdomen and chest has increased by over 300 per cent in the last 5 years. The availability of firearms is directly related to the assault, homicide, and suicide rates[26] and the minimal laws governing the possession of firearms in this country are the prime reason for the increasing problem.

While experience with large numbers of abdominal stab wounds has shown that non-operative management may be employed in up to 50 per cent of patients[4–6,8–17] the same approach has not gained popular acceptance for abdominal gunshot wounds[18–20]. Much of this reluctance has arisen from retrospective reports demonstrating the high incidence of intra-abdominal injuries if the peritoneal cavity has been penetrated[1,20], even in the absence of positive physical findings. In this series 92 of the patients had penetration of the peritoneal cavity and in 82 (89 per cent) there was significant intra-abdominal injury. While this figure is lower than those in other series[1,10,18,20,23] and may be explained by the rather conservative approach to hepatic injury in the present study, it is still double that for patients with penetrating abdominal stab wounds[4,6,8–10]. Nevertheless, there remain over 10 per cent of patients with penetrating gunshot wounds who do not require laparotomy and who may suffer unnecessary morbidity and even death if a policy of mandatory laparotomy is employed.

In contrast to other continents where the average delay from injury to hospital admission is in the region of 30 min[27], patients in this country suffer a prolonged delay before medical care is reached. This has allowed a study of a unique population group. Firstly, it allowed assessment of mortality if definitive care was delayed, analagous to a period of observation if the initial physical findings were equivocal. This delay excluded those patients with critical injuries who died before hospital admission, and inevitably influenced the overall mortality rate in a favourable manner. It did not, however, alter the results of a conservative approach, for all critically injured patients would have required immediate laparotomy. Secondly, it excluded the period immediately following injury when physical signs may be exaggerated by the trauma of having suffered a gunshot wound The mortality rate of 7 per cent in this series compares favourably with other reports[18–20] indicating that delay in operative intervention in patients without critical injury, whether it is due to delayed presentation to hospital or following a period of observation in hospital, is not detrimental. This is confirmed by the fate of the three patients in this study who underwent repeated assessment before laparotomy; not one of them incurred complications.

Peritoneal penetration resulting in significant intra-abdominal injury produced obvious clinical signs in 98 per cent of patients In only two patients was radiological evidence of injury used as a basis for performing surgery. In 97 per cent of patients the decision to operate was made on initial evaluation. This indicates that the vast majority of patients will show a need for surgery on the basis of physical examination alone within 5 h of injury, and that the absence of physical signs outside this time excludes significant injury. A delay in operative intervention because of equivocal physical findings is not detrimental and surgery may be safely postponed until signs of injury are evident, a policy already widely practised when treating abdominal trauma from stab wounds[8–17]. In contrast to abdominal stab wounds very few patients with gunshot wounds present with equivocal clinical findings, and the absence of signs of obvious intra-abdominal injury should be a contraindication to laparotomy. Intra-abdominal injury without penetration of the peritoneal cavity by the bullet has been documented previously even in the context of low-velocity injuries[28,29]. This situation was not encountered in the present series and may be relevant only if the weapon has been fired at close range or with high velocity missiles. In the absence of clinical signs of intra-abdominal injury a policy of observation should be employed in this group of patients.

The distribution of entrance wounds only, and through and through wounds, showed no marked difference between the laparotomy and observed groups. However, all patients with multiple wounds, whether entrance only or through and through, were found to have significant intra-abdominal injury. This indicates the much higher probability of serious injury in this group of patients and, since clinical assessment is difficult, laparotomy is mandatory in this situation.

Nance, in his discussion of Lowe's paper, posed the question, 'What is the correct management of a patient with a through and through abdominal gunshot wound without any clinical signs of injury?'[20]. The five patients in the observed group who sustained this injury indicate that conservative management may be instituted safely. It is difficult to believe that a central through and through wound causes no significant damage but the one patient who presented after 23 h with this injury and without evidence of peritonitis demonstrates that in the absence of physical signs laparotomy is not indicated.

Radiological investigation of patients with abdominal stab wounds is usually limited to an erect chest film, little information being obtained from abdominal radiographs. However, abdominal radiographs are employed routinely in patients with gunshot wounds due to the belief that it is necessary to document the number and position of missiles within the peritoneal cavity[20]. In patients with obvious peritonitis this is a superfluous investigation. Little, if anything, is to be gained from a knowledge of where the missiles lie for the path of a low-velocity bullet is highly unpredictable and a full laparotomy is required. The only preoperative knowledge necessary in this situation is the site of entrance and/or exit wounds. Application of the rule of an odd or even number of wounds then allows an estimation of the number of retained missiles[30] although there are some exceptions. In addition, some of the weapons used in this environment are home-made, and the missiles are not infrequently radiolucent. Abdominal radiography should be limited, therefore, to those patients in whom peritoneal or diaphragmatic penetration is uncertain. In the former, should a bullet be found to lie within the peritoneal cavity, close observation is indicated. If diaphragmatic penetration is confirmed, laparotomy and repair should be undertaken.

Diagnostic peritoneal lavage, although designed initially for blunt abdominal trauma[31–34], has gained popularity in cases of penetrating injury, especially from stab wounds[35–39]. It is still debatable whether the standard quantitative criteria proposed by Perry and Strate[40] can be applied to penetrating trauma. With some modification, diagnostic peritoneal lavage has a useful place in the investigation of patients suffering stab wounds but its use in gunshot victims has been condemned as unnecessary and unreliable[41,42]. This study, along with many others, clearly shows that the vast majority of patients with significant injury present with obvious clinical signs and that further investigation is superfluous.

The results of this prospective trial confirm the high incidence of significant intra-abdominal injury reported in retrospective studies of abdominal gunshot wounds. However, it demonstrates that a policy of selective conservative management is justifiable and safe for those patients without signs of intra-abdominal injury, and delay in intervention until such signs appear does not appear to increase morbidity or mortality. In addition, it confirms the views of other authors from this country that isolated hepatic injuries do not necessarily require operative intervention[16]. Patients with multiple abdominal gunshot wounds merit mandatory laparotomy, but by employing careful and repeated clinical examination a number of other gunshot victims may be spared unnecessary surgery.

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Announcement

Association of Coloproctology of Great Britain and Ireland

On 9 March 1990 The Association of Coloproctology of Great Britain and Ireland was inaugurated at a meeting at The General Hospital, Birmingham. The objective of this multidisciplinary association is to promote the interests, standards and training in Coloproctology.

The officers of The Association are:

President	G. D. Oates
President-elect	N. V. Addison
Honorary Treasurer	R. H. Grace
Honorary Secretary	J. P S. Thomson
Honorary Assistant Secretary	C G. Marks
Representative on the Presidential Board of Surgical Specialties (Royal College of Surgeons of England)	P. F. Schofield
Representative on the European Council of Coloproctology	R. J. Nicholls

The constitution and an application form (if not attached) may be obtained by writing to the Honorary Secretary, The Association of Coloproctology of Great Britain and Ireland, The Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK.

The Council will be elected by the officers at a meeting on 27 June 1990. The council will then meet in September. The first clinical meeting with the Annual General Meeting will be held during the summer of 1991. It is anticipated that Regional Chapters will be developed during the first year.

Applications for associate membership, membership and senior membership should be made to the Honorary Secretary at the above address as soon as possible so that they will be available for the meeting on 27 June 1990.

Further information may be obtained from James P. S. Thomson, St Mark's Hospital, City Road, London EC1V 2PS, UK; telephone 01-253 1050 ext. 4045.

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Prospective study of the value of ultrasound measurements in the diagnosis of acute rejection following renal transplantation

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In this prospective study we have used ultrasonographic measurements of the cross-sectional area of transplanted kidneys, as an objective assessment of graft size, for diagnosis of acute rejection episodes. Sixty episodes of acute graft dysfunction (serum creatinine rise of ≥30 μmol/l) were studied in 40 patients. Tru-Cut® biopsy under ultrasound control was performed in all cases and 36 episodes of acute cellular rejection were identified. An increase in graft cross-sectional area of ≥10 per cent was defined as a positive scan, indicative of an acute rejection episode. Using these criteria, ultrasound correctly diagnosed rejection in 29 out of 36 cases (sensitivity 81 per cent) and there were four false positive results (specificity 83 per cent). The investigation had a predictive value of 88 per cent when positive and 74 per cent when negative.

Keywords: Kidney transplantation, renal allograft rejection, ultrasound

Acute rejection is the most important cause of graft dysfunction after renal transplantation. Although the clinical assessment of graft size by palpation can be helpful in reaching a diagnosis of rejection, it is too subjective to be relied upon Furthermore, the widespread use of cyclosporin has made the clinical diagnosis of acute rejection more difficult in two ways. First, the pyrexia and graft tenderness associated with a rejection episode are less marked in cyclosporin treated patients and, second, cyclosporin induced nephrotoxicity must also be considered in the differential diagnosis of deteriorating graft function. In this study ultrasonographic measurements of renal transplant cross-sectional area have been performed in an attempt to achieve a more objective method of estimating graft size. The method was used to identify significant graft swelling as an indicator of an ongoing acute rejection episode.

Patients and methods

For the purposes of this study, acute graft dysfunction was defined as a rise in serum creatinine of ≥30 μmol/l between two successive estimations. During the period January 1988 to April 1989, 60 consecutive episodes of acute renal allograft dysfunction were studied in 40 patients. In each case ultrasound measurement of renal allograft cross-sectional area was used as an assessment of overall allograft size.

The best quality ultrasound images were obtained when the transplanted kidney was close to the skin and so, if possible, the transplant kidney was placed in a subrectus pouch with its long axis parallel to the wound, its convex surface towards the midline and the vessels facing laterally. It must be stressed, however, that not all transplants will lie in this position and scanning can be successfully performed with the organ in any other orientation. The use of a subcuticular suture to close the skin and an Opsite® (Smith and Nephew Ltd, Hull, UK) dressing to cover the wound facilitated ultrasound in the early days after operation.

Transplanted kidneys were scanned daily from the first day after surgery until discharge from hospital Subsequent scanning was performed in the transplant clinic at variable intervals, but for episodes of deteriorating graft function, daily scanning was reinstituted.

All scans were performed by the same experienced ultrasonographer (A.B) using an Aloka SSD-630 (Keymed, Southend-on-Sea, UK) realtime ultrasound machine fitted with a 3 5 MHz linear array probe. After recognizing the longitudinal and transverse axes of the kidney, the ultrasound probe was lined up over the hilum to demonstrate a transverse cross-section (*Figure 1*). A hand guided cursor was used to trace the outline of the kidney substance and from this the machine calculated and displayed the area of the cross section in cm^2 Four measurements of cross-sectional area were made each day and these values and their mean were recorded

Two reference points were used in order to be able to identify the same cross-section at subsequent scans. The first was usually the point at which the vessels emerged from the hilum and the second was usually a prominent vessel within the renal parenchyma. On each occasion a hard copy of this reference cross-section was made as a further method of subsequent identification

In all cases of acute dysfunction studied a transplant biopsy was performed under ultrasound control using a Tru-Cut® (Travenol Laboratories, Deerfield, Illinois, USA) needle mounted in a Biopty® (Radiplast, Uppsala, Sweden) gun This method allows very precise introduction of the biopsy needle into the renal cortex with a very low morbidity Histological diagnoses of acute rejection, acute tubular necrosis, transplant glomerulopathy, ischaemia, chronic rejection and recurrent disease were made by two experienced consultant histopathologists with an interest in renal pathology.

The results of urine culture and whole blood cyclosporin levels were also available to help with diagnosis Cyclosporin nephrotoxicity was diagnosed: (1) on clinical grounds as a rise in serum creatinine of ≥30 μmol/l between two consecutive estimations followed by a return to baseline level after a 30 per cent cyclosporin dose reduction; (2) when blood cyclosporin levels were in excess of 600 ng/ml, and (3) when there was an absence of an acute cell infiltrate in the biopsy.

Previous studies in this unit have demonstrated that ultrasound measurement of graft cross-sectional area is highly reproducible and that an increase in cross-sectional area of 10 per cent or more is a significant increase in transplant size[1,2]. A scan showing such an increase is referred to as a positive scan and is suggestive of an acute rejection episode. The value of ultrasonography was assessed by comparing scan results against the results of the other investigations.

Cases of acute pyelonephritis or urinary tract infection and ureteric obstruction have been shown to be a source of false positive scans. Therefore cases of graft dysfunction associated with a positive urine culture or ultrasound evidence of pelvicalyceal dilatation suggestive of obstruction were excluded from analysis.

Results

An example of the ultrasound findings in acute rejection is shown in *Figure 2*. Individual values of the percentage change in cross-sectional area for each of the 60 episodes of acute graft dysfunction are shown in *Figure 3*. Thirty-six episodes of acute cellular rejection were identified and in 29 of these the ultrasound scan was positive, with values ranging from +11 per cent to +55 per cent. In seven cases the scan was falsely negative (sensitivity 81 per cent). In 21 of the 24 cases

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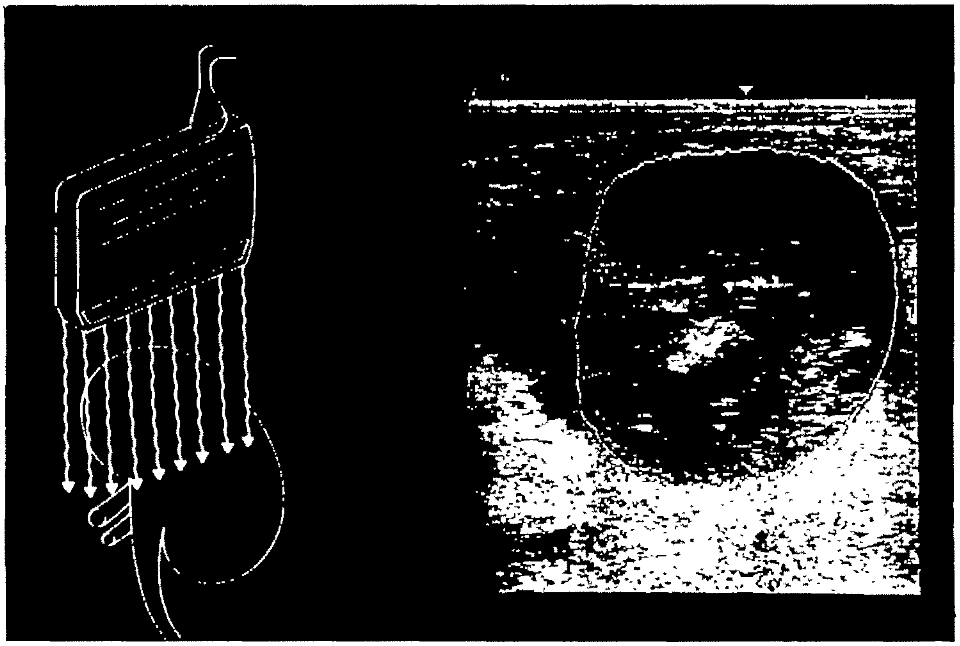

Figure 1 *The technique of measuring renal transplant cross-sectional area using ultrasound. The ultrasound probe is lined up to demonstrate a transverse cross-section of the kidney at the hilum. A hand guided cursor is used to trace the outline of the organ and the machine calculates and displays the cross-sectional area in* cm^2

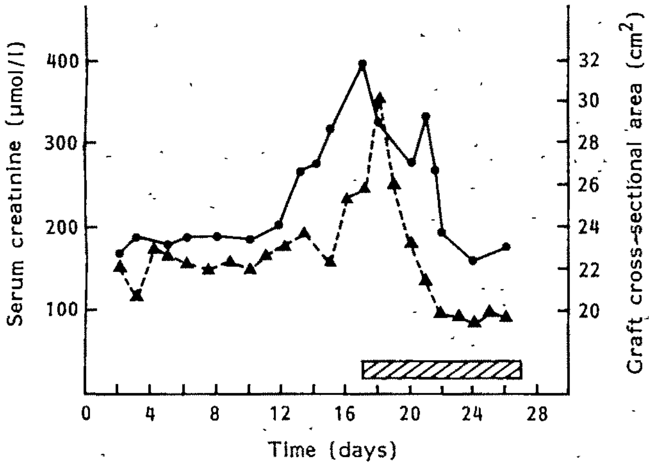

Figure 2 *Ultrasound changes in cross-sectional area during the second rejection episode in a 25-year-old female transplant recipient. There is a marked increase in cross-sectional area which falls back to the baseline after successful treatment with the monoclonal antibody OKT3 (Cilag Limited, High Wycombe, UK).* ●—●, *Cross-sectional area* (cm^2), ▲—▲, *creatinine* (µmol/l); ■, *OKT3*

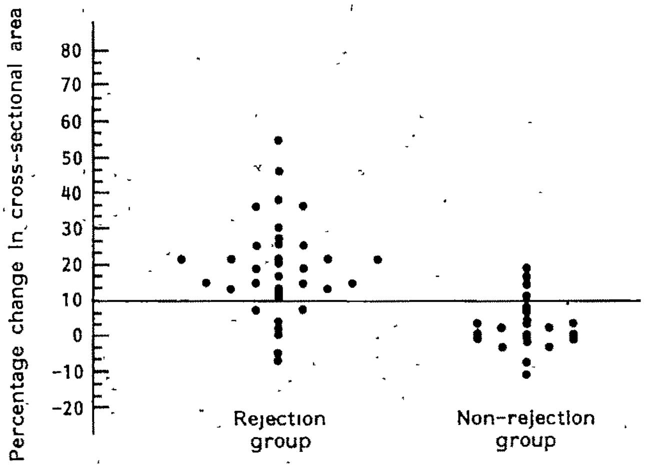

Figure 3 *Individual changes in transplant cross-sectional area in 60 cases of acute graft dysfunction The +10 per cent diagnostic level which suggests acute rejection is shown*

of acute allograft dysfunction not due to acute rejection the following diagnoses were made: cyclosporin toxicity ($n=8$), acute tubular necrosis ($n=8$), transplant glomerulopathy ($n=2$), ischaemia ($n=1$), chronic rejection ($n=1$) and recurrent glomerulonephritis ($n=1$). In the remaining three cases in this group although rejection was excluded no specific diagnosis was made. In the non-rejection group there were 20 true negative and four false positive scans (specificity 83 per cent). The predictive value of ultrasound scanning when positive was 88 per cent and when negative was 74 per cent.

Discussion

Despite recent advances in immunosuppression, rejection remains a central problem in renal transplantation and there has been considerable interest in developing techniques of early diagnosis. Tru-Cut biopsy[3], fine needle aspiration biopsy[4] and intrarenal manometry[5] have all been used with success, but are invasive. In this unit ultrasound measurement of transplant cross-sectional area has been used as a non-invasive method of diagnosing rejection.

It has long been realized that ultrasound scanning could be used in the assessment of renal transplants. The earliest studies concentrated on qualitative features and cortical thickness[6], distinctiveness of the corticomedullary junction[7], medullary pyramid size[8], texture of the sonic architecture[9] and renal sinus echoes[10] have all been proposed as useful parameters for diagnosing rejection. Improvements in ultrasound technology have made possible the measurement of renal size. Graft diameter was the first parameter to be studied but there was poor correlation with clinical findings[11]. Measurement of renal cross-sectional area then became possible and, by making serial cuts of the kidney, renal volume could be calculated[12]. Volume measurement proved to have a considerable inherent inaccuracy because of the summation of individual errors in measuring each cross-sectional area. This method is also very time consuming and in the present study cross-sectional area alone was used as a reflection of renal size. Other workers have advocated using a mixture of qualitative and quantitative parameters[13,14].

There are sound theoretical reasons which suggest that ultrasound measurement of renal size should be useful in the diagnosis of deteriorating allograft function. During an acute rejection episode cellular infiltration and interstitial oedema cause graft swelling. This is sought clinically by palpation, but ultrasound scanning is a more objective and accurate assessment of change in size. We have demonstrated that marked increases in transplant cross-sectional area can occur as a consequence of rejection and that an increase of greater than 10 per cent predicts rejection with a high degree of accuracy.

All other differential diagnoses were found not to be associated with an increase in graft cross-sectional area and these findings are also explicable on theoretical grounds. Chronic rejection produces ischaemia and fibrosis and would be expected to cause a decrease in renal size. Similarly, cyclosporin toxicity, by causing an arteriolopathy leading to reduction in renal blood flow, might be expected to cause a reduction in transplant size. Present data did not consistently show a reduction in renal cross-sectional area in cases of chronic rejection or cyclosporin toxicity, but the lack of a significant increase in size was enough to allow acute rejection to be distinguished from these pathologies Cyclosporin induced nephrotoxicity is sometimes difficult to diagnose. The measurement of blood cyclosporin levels is of some help in making this diagnosis[15], but we have not found these to be sufficiently reliable and have largely based the diagnosis on clinical grounds. However, ultrasound examination can be helpful by excluding acute rejection. Continuous wave Doppler ultrasonography has recently been used as a method of diagnosing cyclosporin toxicity by quantifying the associated decrease in graft perfusion[16]. The use of combined conventional and Doppler ultrasound in the assessment of graft dysfunction is worthy of further study. Acute tubular necrosis with consequent hyperaemia and oedema might be expected to cause an increase in graft size, but in the present study there was no evidence of this and, indeed, it was possible to differentiate this process from acute rejection using ultrasound criteria

In parallel with a falling creatinine it was found that decreasing graft size was a useful method of monitoring the completeness of response to antirejection therapy. The graft is expected to return to baseline size with complete resolution of the rejection process (*Figure 2*)

All scans in this series were performed by the same experienced ultrasonographer and this is particularly important in achieving a high level of reproducibility. Both ultrasonographer and ultrasound machine, which is housed in its own room in the transplant unit, are exclusively dedicated to transplant patients. Modern ultrasound machines are expensive which has obvious resource implications. Our ultrasound machine is not used simply for the assessment of graft dysfunction; it is also used in the investigation of ureteric obstruction, vascular complications of transplantation and for ultrasound guided renal biopsy. We believe it to be cost effective.

This study has demonstrated that ultrasound measurement of transplant cross-sectional area is highly specific in differentiating acute rejection episodes from other causes of deteriorating allograft function. Although seven false negative scans occurred, the sensitivity of 81 per cent is high enough to make ultrasonography a useful adjunct in the diagnosis of acute rejection. The method is quick, reproducible and non-invasive. It is worthy of further study and more widespread use

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Axillofemoral bypass as a limb salvage procedure in high risk patients with aortoiliac disease

Thirty-eight patients presenting with severe limb ischaemia and considered unfit for major aortic reconstruction underwent axillofemoral bypass as a limb salvage procedure. Four patients (11 per cent) died, including two who had presented with bilateral ischaemia secondary to acute aortic occlusion. The operative mortality rate for patients presenting with rest pain or ulceration/gangrene was 6 per cent. Cumulative 5-year survival and limb salvage were 44 per cent and 86 per cent respectively. Graft occlusion was the principal cause of worsening symptoms during follow-up (5-year primary patency of 68 per cent) and accounted for all major amputations of the operated limb. Axillounifemoral grafts had a significantly worse 5-year patency (50 per cent) than axillobifemoral grafts (80 per cent, P<0·05) and three of five patients who developed worsening symptoms in the non-operated limb died or required a major limb amputation as a consequence. Axillofemoral bypass is a valuable alternative to major aortic reconstruction in elderly patients and allows a greater proportion to be offered reconstruction than would otherwise be possible.

Keywords: Limb salvage, aortoiliac disease, axillofemoral bypass

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High risk patients presenting with ischaemic rest pain, ulceration or gangrene as a consequence of aortoiliac segment disease pose a management dilemma. While angioplasty and femorofemoral bypass may be appropriate for some, bilateral iliac disease and inaccessible stenoses may require some form of proximal reconstruction in order to salvage the limb. Over the past 10 years, axillofemoral bypass was performed as a primary limb salvage procedure in 38 patients with severe aortoiliac disease, all of whom were considered unfit for aortofemoral bypass. This retrospective review was carried out to assess the acceptability of this form of management in terms of operative mortality, relief of symptoms, long-term patency and limb salvage.

Patients and methods

A retrospective study was undertaken of the case records and follow-up of 38 consecutive patients undergoing axillofemoral bypass to 55 limbs between January 1975 and December 1984 There were 23 men (age 54–77 years, mean 67 years) and 15 women (age 57–81 years, mean 70 years). Seventeen (45 per cent) presented with rest pain, 19 (50 per cent) presented with ulceration or gangrene, and two (5 per cent) presented as emergencies with severe bilateral ischaemia following acute aortic occlusions A further six patients underwent axillofemoral bypass during the same time period but have not been included in this study Three of these operations were for claudication and three for complications following aortofemoral bypass Preoperative angiography was undertaken in 79 per cent of patients; five (13 per cent) showed aortic occlusion and the remainder had severe bilateral stenotic or occlusive disease of the aortoiliac segment. Superficial femoral artery occlusion was present in 65 per cent of operated limbs, profunda femoris occlusion or stenosis in 18 per cent, and 67 per cent had diseased vessels below the knee.

All patients had been deemed unfit for aortic reconstruction by the anaesthetic and vascular services and a summary of preoperative risk factors are detailed in *Table 1*. Data for patients undergoing aortofemoral bypass and aortoiliac endarterectomy during the same period have been included for comparison. Sixty-six per cent of axillofemoral patients presented with two or more risk factors, compared with 19 per cent and 12 per cent undergoing aortofemoral bypass and aortoiliac endarterectomy respectively. Half of the axillofemoral patients had had previous vascular surgery.

Axillofemoral bypass was performed in the manner described by Blaisdell and Hall[1] and Sauvage and Wood[2] under systemic antibiotic cover (a cephalosporin). The graft was tunnelled from the axilla to the ipsilateral groin, where an end-to-side anastomosis was made to the superficial femoral and profunda femoris arteries or an end-to-end anastomosis was made to effect a profundaplasty If a bilateral procedure was required, a second graft was anastomosed end-to-side to the main graft, tunnelled subcutaneously across the lower abdomen, and anastomosed to the contralateral femoral artery All anastomoses were made using 5/0 polypropylene. Unilateral bypass was performed in 21 patients and axillobifemoral bypass in 17. Standard thickness Gore-tex® (W L Gore and Associates (UK) Ltd, Livingston, UK) was used in 33 patients (6 mm diameter in five cases, 8 mm diameter in 28 cases) and 8 mm diameter Dacron® (E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA) was used in five cases Six patients had synchronous procedures including femoropopliteal (Gore-tex) bypass (one case), iliac thrombectomy (one case), toe amputation (two cases), below knee amputation (one case) and lumbar sympathectomy (one case).

Patients were regularly reviewed at the vascular clinic, although where long distances precluded attendance, the family doctor completed a questionnaire Follow-up ranged from 2 to 107 months, mean 40 months. Two patients were lost to follow-up after 2 and 9 months respectively. Primary patency refers to the time from operation to first occlusion, death or last follow-up Secondary patency includes successfully thrombectomized grafts in the patent group. Patients requiring a major limb amputation, either as a synchronous procedure or within 30 days of bypass, have been regarded as failures in the limb salvage statistics Statistical analysis was performed using the log rank and χ^2 tests

Results

Four of 38 patients (11 per cent) died within 30 days of operation from myocardial infarction (one case), bronchopneumonia (two cases), or upper gastrointestinal haemorrhage (one case), including both patients who presented with severe lower limb ischaemia secondary to acute aortic occlusion. The

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Table 1 *Preoperative risk factors in patients undergoing aortoiliac reconstruction in Aberdeen between 1974 and 1984*

	Axillofemoral bypass	Aortofemoral bypass	Aortoiliac endarterectomy
Number of patients	38	245	57
Mean age (years)	68	60	53
Ischaemic heart disease (%)	82	29	16
Treated hypertension (%)	50	22	19
Stroke or transient ischaemic attack (%)	34	4	4
Diabetes mellitus (%)	13	7	9
Pulmonary embolus (%)	10	0	0
Polycythaemia (%)	10	2	4
Previous vascular procedures (%)	50	16	5

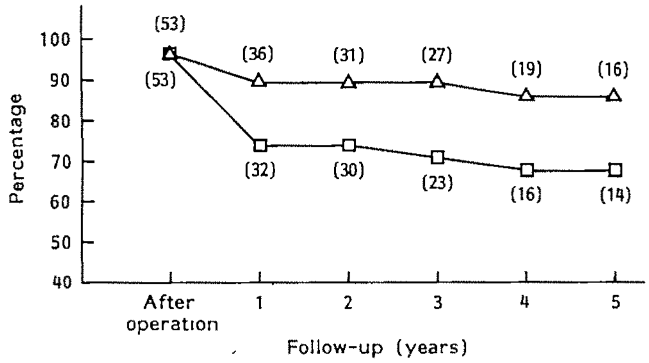

Figure 1 *Cumulative primary limb patency and limb salvage following axillofemoral bypass Values in parentheses indicate the number of limbs at risk,* □, *primary limb patency;* △, *limb salvage rate*

'elective' mortality rate for those presenting with rest pain, ulceration or gangrene was therefore two of 36 patients (6 per cent). Six survivors (18 per cent) suffered non-fatal postoperative complications. graft occlusion (two cases), myocardial infarction (one case), graft seroma (three cases). Four patients required further surgery within 30 days of operation. Three patients required amputation because of lack of improvement in preoperative ischaemia (one below knee amputation and two amputations of toes) and one patient had a phenol sympathectomy following early graft thrombosis.

Sixteen patients died during follow-up (range 2–86 months, mean 38 months), giving a cumulative survival of 84 per cent and 66 per cent at 1 and 2 years respectively, but only 44 per cent at 5 years. Ten of the late deaths were cardiovascular in origin: myocardial infarction (six cases), stroke (two cases) and mesenteric infarction (two cases). One patient died as a direct consequence of repeated graft occlusion.

Cumulative primary limb patency and limb salvage are detailed in *Figure 1* Including the early postoperative occlusions, 12 patients suffered 15 episodes of thrombosis involving 17 grafted limbs, with 12 episodes occurring within the first 12 months of operation. Two grafts thrombosed in the early postoperative period to give an immediate patency of 96 per cent. No active intervention was undertaken in one patient with poor runoff vessels, while a chemical sympathectomy was performed in the second. Neither patient died nor required a major limb amputation as a consequence of early graft thrombosis. Ten patients suffered a total of 13 episodes of late graft thrombosis affecting 15 grafted limbs. Thrombectomy was done in seven cases and was successful in five cases, although two have subsequently re-occluded. Primary limb patency was 74 per cent at 1 year and 71 per cent and 68 per cent at 3 and 5 years respectively. Thrombectomized grafts remained clear for 1–31 months (mean 8·4 months) with secondary patencies of 79 per cent, 79 per cent and 72 per cent at 1, 3 and 5 years respectively. Unilateral grafts had a poorer 5-year primary limb patency (50 per cent) than axillobifemoral grafts (80 per cent, $P<0{\cdot}05$). In six episodes of late graft occlusion, no attempt was made to clear the graft. Two occlusions occurred in the postoperative period after an earlier thrombectomy, two were found at review at the vascular clinic having developed a satisfactory collateral circulation, and two were referred late with extensive peripheral gangrene requiring below knee amputation. During late follow-up, four patients required six major amputations, two of which were of the non-operated limb in patients with a unilateral bypass. All major amputations involving the operated limb followed occlusion of either proximal or femoropopliteal grafts. Cumulative limb salvage was 89 per cent at 1 year and 86 per cent at 5 years.

Rest pain was relieved in 81 per cent of survivors and ulcer healing and improvement in digital ischaemia occurred in 74 per cent. During follow-up, 12 patients developed worsening symptoms (seven in the operated limb, two in the non-operated limb and three in both limbs) Worsening symptoms in the operated limb were always associated with graft occlusion, one patient died and three required major amputation. Two of the five patients with worsening symptoms in the non-operated limb underwent femorofemoral bypass with synchronous femoropopliteal bypass. One died of mesenteric infarction after lumbar sympathectomy and two required major amputation.

Discussion

Less than 10 per cent of current workload involves patients with severe limb ischaemia due to potentially reconstructible aortoiliac disease who are unfit for aortofemoral bypass and unsuitable for either angioplasty or femorofemoral bypass Despite much co-existent infrainguinal disease, revascularization of the femoral and, in particular, the profunda femoris vessels from the axillary artery may be the only alternative to death or amputation. An axillofemoral bypass may also enable healing of a digital or forefoot amputation, and could mean the difference between primary healing of a below knee amputation and revision to an above knee amputation.

It has been our policy, particularly since acquiring digital subtraction angiogram equipment, to perform preoperative angiography in as many patients as possible. In 21 per cent, bilateral absence of femoral pulses precluded a transfemoral approach, and in these patients groin exploration and on-table angiography before axillofemoral bypass was considered preferable to translumbar aortography.

The overall operative mortality rate was 11 per cent. For patients presenting with rest pain, ulceration or gangrene, the mortality rate (6 per cent) was no different from that following aortofemoral bypass (6 per cent) for patients presenting with similar symptoms[3]. Five-year survival following axillofemoral bypass, however, was poor (44 per cent) compared with that of aortofemoral bypass (72 per cent)[3] for limb salvage and reflects the higher incidence of generalized vascular disease in the former group. It is worthy of note, however, that rest pain and distal ischaemic lesions were improved in the majority of survivors who had a 5-year operated limb salvage rate of 86 per cent.

Graft occlusion was the principal source of late morbidity[4] and accounted for all the worsening symptoms and major amputations of the operated limb. Patients are now recommended to check regularly for graft pulsation and report immediately to their doctor if they experience worsening symptoms. Graft thrombectomy was not usually attempted in the earlier years of the study. However, the morbidity and mortality associated with occlusion has now led to a more aggressive policy of thrombectomy (repeated when necessary, with reconstruction of the distal anastomosis if this was the underlying cause of failure) in order to maintain limb viability for as long as possible. Patients referred late, with no evidence of severe limb ischaemia, are managed conservatively on the assumption that a satisfactory collateral circulation has developed. Results suggest that bifemoral grafts have a better long-term patency than unifemoral grafts, presumably because of the increased rate of flow in the former[5]. For this reason, and because of morbidity and mortality associated with the development of ischaemia in the non-operated limb, bilateral reconstruction is now advocated in patients with claudication or asymptomatic iliac stenosis or occlusion in the opposite limb to that in which the operation is primarily indicated.

In conclusion, experience suggests that axillofemoral bypass is a valuable alternative to major aortic reconstruction in a small group of elderly, high risk patients with critical limb ischaemia. Nevertheless, it is a compromise Aortofemoral bypass remains the mainstay of management[6].

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Anatomical aspects of the blood supply to the skin of the posterior calf: technique of below-knee amputation

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Whether or not the soleus muscle should be excised during below-knee amputation is a point of contention. The anatomical basis for the blood supply to the skin of the posterior calf has been examined by dissection and selective arterial injection of cadavers. The results showed that the skin used to construct the posterior flap for below-knee amputation derives its blood supply from both axial vessels, running with the peripheral nerves, and perforating vessels arising through the gastrocnemius muscle. There is no contribution by blood vessels that pass through the soleus muscle. When a posterior flap for below-knee amputation is constructed the soleus muscle should be completely excised.

Keywords: Amputation, arterial anatomy

Despite advances in distal reconstruction of arteries in the leg, for a number of patients the final outcome of severe ischaemia remains amputation, which should be below the knee if possible[1,2]. Given the poor blood supply to the limb overall it is to be expected that wound healing would be precarious and that aspects of the surgical technique would be important in determining the result. The expected healing rate will naturally govern the frequency with which below-knee amputation is attempted, and centres with a long-standing interest in amputation techniques have reported that below-knee amputation can be performed successfully in 60–75 per cent of patients who require leg amputation for ischaemia[3], with reamputation in 5–15 per cent[3–7].

However, these results are not necessarily typical of practice throughout the UK, as in Oxford we noted a deterioration in our below-knee amputation results between 1978[8] and 1984[9]. In the latter study only 33 per cent of leg amputations were performed below the knee, with 28 per cent of these requiring reamputation. These poor results prompted an investigation of the surgical technique used to perform below-knee amputation and comparison with other described techniques.

A crucial element of modern below-knee amputation technique has been the more or less universal adoption of a long posterior 'myoplastic' flap[5,10], as popularized by Burgess *et al.*[11]. The healing of this flap is critically dependent upon the blood supply. After studying a number of textbooks and published techniques of below-knee amputation[5,11–14], considerable differences were noted in the various descriptions of how the posterior flap should be constructed, particularly with reference to the inclusion or removal of the soleus muscle, which forms the bulk of the muscle in the posterior compartment of the leg at this level. The term myoplastic assumes that the blood supply of the flap arises from the muscle, although the term musculocutaneous is now preferred[15] and, if this were the case, excision of the underlying muscle would be detrimental to flap survival. On the other hand, if the blood supply were not derived via the muscle then the retention of a large muscle such as the soleus would make the flap unnecessarily long and bulky, which might also be expected to prejudice flap survival.

We were unable to find a detailed description of the normal route of blood supply to the skin of the posterior calf in standard anatomical texts or descriptions of below-knee amputation techniques. Furthermore, although the anatomy of the blood supply to the skin in this area has been recently described in detail from the point of view of constructing musculocutaneous flaps[15–18], these studies have concentrated on flaps for reconstructive plastic surgery and do not specifically examine the anatomy from the point of view of below-knee amputation and the contribution of the soleus muscle. An anatomical study in cadavers was therefore undertaken.

Materials and methods

Conventional dissections were performed on six cadaver limbs which were without evidence of significant vascular disease. Flaps were raised using a vertical midline calf incision down to and through the deep fascia. Blood vessels seen to run down under the deep fascia were traced proximally, continuing the dissection until the junction with the popliteal vessels was reached. Connections passing deeply into the muscle were noted.

Selective arterial injection studies were carried out in 16 further cadaver limbs, of which 11 were technically completely satisfactory. All limbs were without evidence of significant vascular disease. Without preliminary dissection, other than that required for arteriotomy, a 6 Fr gauge Fogarty balloon catheter was introduced into either the superficial femoral artery in the lower thigh ($n=1$) or the posterior tibial artery at the ankle ($n=8$). The catheter was then advanced and by comparison to external measurement the balloon was placed in the midpopliteal artery and the catheter was tied firmly in place by a ligature placed at the arteriotomy.

A blue-coloured, radio-opaque, solidifying compound for injection was prepared by dissolving gelatine in 16 ml distilled water at 100°C until saturated and then mixing in 145 ml Micropaque® (Nicholas Laboratories Ltd., Slough, Berkshire, UK) barium powder (230 per cent weight/volume) and 0·16 g methylene blue dye. After cooling, the resultant mixture was warmed in a water-bath and 120 ml was injected using a 60 ml syringe connected by a screw-lock to the catheter to allow maximum manual pressure to be exerted. Injections were performed via an 8 Fr gauge umbilical catheter using the separate occluding balloon catheter positioned in three ways to allow selective filling of different branches of the popliteal artery as follows:

1. The umbilical catheter was inserted via the superficial femoral artery (which was tied off proximally) so as to place the catheter tip in the midfemoral artery. No balloon catheter was inserted. Injection would be expected to fill all branches of the popliteal and lower leg arteries ($n=2$).
2. The Fogarty balloon catheter was inserted via the superficial femoral artery and placed so as to occlude the midpopliteal artery. The umbilical catheter was inserted via the posterior tibial artery. Injection via the umbilical catheter would be expected to fill retrogradely branches of the lower popliteal and lower leg arteries only ($n=1$).
3. The Fogarty balloon catheter was inserted via the posterior tibial artery and placed so as to occlude the midpopliteal artery. The

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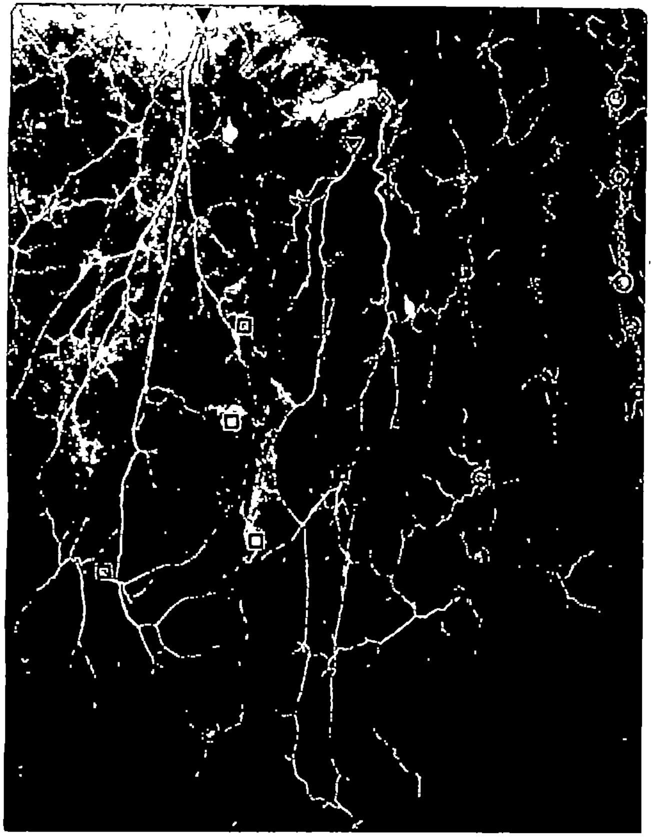

Figure 1 *Radiograph of lower leg skin flap after injection of contrast/gelatin mixture into the midfemoral artery without a distal obstructing balloon.* ▼, *Saphenous artery (axial vessel);* ▽, *sural artery (axial vessel);* ◇, *artery following sural communicating and lateral cutaneous nerve of calf (axial vessel); and* ○, *four rows of septal perforating vessels, from left to right: (1) perforator row along medial border of tibia, derived from posterior tibial artery; (2) perforator row along posterior peroneal septum derived from peroneal artery; (3) perforator row along anterior peroneal septum, derived from anterior tibial artery, (4) perforator row along lateral border of tibia derived from anterior tibial artery; and* □, *random perforators derived from vessels passing through gastrocnemius muscle belly*

superficial femoral artery was exposed in the upper thigh and cannulated with an umbilical catheter. Injection via the umbilical catheter would be expected to fill branches of the upper popliteal artery only ($n=8$).

After injection the dissection was commenced by raising a long posterior calf flap from a circumferential incision just above the ankle and a single longitudinal incision along the subcutaneous surface of the tibia. The deep fascia was raised with the flap. The site and position of injected vessels running in the flap was noted and injected perforating vessels from the gastrocnemius and soleus muscles were both noted and explored to determine their origin. Radiographs of the flap were then obtained *in situ* using high definition film (Singul-X® RP non-screen, C.E.A. (UK) Ltd., Leighton Buzzard, Bedfordshire, UK). Finally the vessels running into the flap from above were traced back to their origins at the main vessels. Immediately after the dissection a diagram of the blood supply of the specimen was drawn and labelled.

Results

The blood supply of the skin of the posterior calf was found to arise from three sources (*Figure 1*). The first source was an axial supply which was derived from vessels that arose from either the popliteal artery or the popliteal branches to gastrocnemius and ran with the cutaneous nerves. All specimens had at least three such vessels. A constant artery was found to pass to and then to run with the saphenous vein and nerve. A more variable artery passed to and then ran with either the sural, sural communicating or lateral cutaneous nerve of the calf. These vertical arteries ran adjacent but superficial to the deep fascia and gave rise to lateral branches that formed a network under the entire flap, and to branches that passed superficially to nourish the skin at irregular intervals.

The second source of blood supply was perforating vessels arising in four approximate lines which supplied the lateral and medial skin of the calf, but not the posterior skin: (a) three rows of posterolateral septal perforators, five or six in number, arising from the anterior tibial and peroneal arteries along the lateral border of the tibia, along the anterior peroneal septum and along the posterior peroneal septum; and (b) one row of anteromedial septal perforators, six or seven in number, arising from the posterior tibial artery, forming a row along the medial border of the tibia.

The third source was midposterior perforators, two to seven in number, randomly arranged, and all arising from the vessels within the gastrocnemius muscle belly.

In no case was the skin of the posterior calf supplied by vessels arising from or passing through the soleus muscle. Furthermore, balloon occlusion of the popliteal artery to prevent filling of the four rows of distal septal perforators did not appear to compromise the supply to the posterior calf skin via the axial supply and gastrocnemius perforators (*Figure 2*).

Discussion

Recent advances in our understanding of the blood supply of the skin of the limbs have shown that it arises from two sources: axial vessels, usually accompanying cutaneous nerves that run the length of the limb, and perforating vessels, running to the skin via intermuscular septae[15,18]. The findings of this study are in broad agreement with those of Haertsch[18] and Cormack and Lamberty[15]. These authors describe axial vessels to the posterior calf running with (1) the saphenous nerve (the

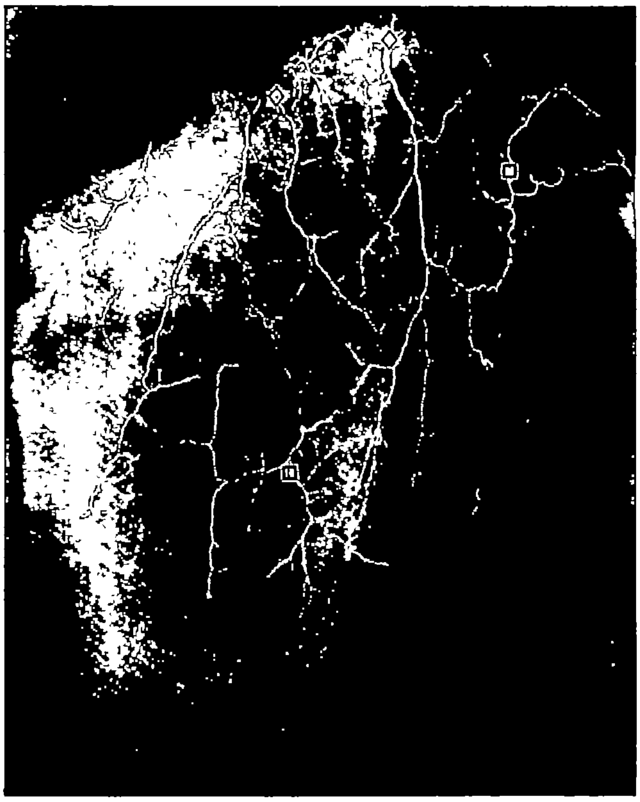

Figure 2 *Radiograph of lower leg skin flap after injection of contrast/gelatin mixture into the femoral artery in the upper thigh, with a distal obstructing balloon placed in the midpopliteal artery.* ▼, *Saphenous artery (axial vessel);* ◇, *branches direct from the popliteal artery running with the sural nerve and lateral cutaneous nerve of the calf (axial vessels), and* □, *random perforators arising from vessels running through the gastrocnemius muscle belly*

saphenous artery, a branch of the descending genicular) and (2) the sural, sural communicating and lateral cutaneous nerves of the calf (the superficial medial, median and lateral sural arteries) In the upper posterior calf a few perforators derive from the blood supply to the gastrocnemius, itself derived from the sural arteries. In the lower leg, below the level of the usual amputation flap, medial and lateral septal perforating vessels derive from the anterior tibial, posterior tibial and peroneal arteries. The soleus is stated to obtain its blood supply also from the lower popliteal, peroneal and posterior tibial arteries, but the contribution of vessels passing through the soleus to the overlying skin flap is not described.

The present study shows that in the normal leg the soleus muscle makes no contribution to the blood supply of the posterior skin flap used for below-knee amputation. Patients undergoing below-knee amputation for occlusive vascular disease do not, of course, have normal vasculature, but in the main it is the major vessels such as the popliteal artery and its immediate branches that are occluded, while the smaller vessels remain patent. Indeed, the axial blood vessels such as the superficial sural and saphenous arteries may become even more important in this case.

Since the soleus muscle does not contribute to the blood supply of the flap the implication is that the muscle should be entirely excised Failure to do this will result in an enlarged bulbous stump, with the skin flap required to cover the circumference of the stump unnecessarily lengthened and possibly under tension, a recipe for failure of healing. The procedure of 'bevelling' the muscle that is described in some texts lessens the size of the stump, but leaves behind unnecessary muscle that is possibly devitalized because the bevelling process is likely to remove the posterior tibial and peroneal arteries that supply the soleus muscle (which may already be occluded).

In the past, when prostheses were end-bearing, a large bulk of muscle covering the severed bone might have been an advantage, but modern below-knee prostheses take much of the weight on the prepatellar tendon and a bulky stump is a positive disadvantage to obtaining a snug, stable fit.

In conclusion, there are logical reasons for advising excision of the soleus muscle from the posterior flap during below-knee amputation. Since 1986 we have included excision of the soleus muscle in our technique, and this has been associated with a marked improvement in results. We believe the advice to excise the soleus is likely to be no surprise to those surgeons performing below knee amputation in centres recognized to have the best results, but the term 'myoplastic flap' may have led less experienced surgeons to assume that the soleus muscle must be retained. Perhaps the term 'myoplastic flap' should be discarded We would speculate that this technical point may have contributed to poor results of below knee amputation performed in non-specialist centres and district general hospitals. Although there is little direct evidence of poor results in district general hospitals, other than our own study[9], the national average percentage of major limb amputations performed below the knee is 43 per cent, and in some regions this falls to 27 per cent, suggesting that the results of below knee amputation in these regions may be poor[19]. Indeed, it is of interest that until relatively recently below-knee amputation was thought to have little chance of healing[20], until Kendrick produced a remarkable series of successful amputations for which he used skin flaps from which all the muscle was excised[21], demonstrating the adequacy of the axial blood supply

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Lymph node metastasis from melanoma with an unknown primary site

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Twenty-six patients, treated surgically between 1961 and 1986 because of lymph node metastasis from melanoma with an unknown primary, were analysed. Six patients had a history of spontaneous regression of a skin lesion. Following node dissection, the overall actuarial disease-free survival rate was 49 per cent, after both 5 and 10 years. When considered as single factors, female (versus *male*), *one lymph node involved* (versus *more than one node involved*) *and site of metastasis in the groin or axilla* (versus *the neck*) *were found to have significantly favourable effects on prognosis with 5-year survival rates of 82 per cent (25 per cent), 82 per cent (27 per cent) and 80 per cent (11 per cent) respectively. However, at multifactorial analysis only the site of cervical metastases maintained a significant influence on survival* (P = 0·005). *As survival in this series is comparable with, or even better than, that of adequately treated patients with lymph node metastasis from a known primary melanoma, a radical node dissection is essential also in these patients.*

Keywords: Unknown primary, melanoma, lymph node metastasis, spontaneous regression

During the course of malignant disease a patient sometimes presents with metastases from an unknown primary tumour site In 50 per cent of such cases the metastases are localized in lymph nodes[1]. In melanoma patients the problem of an unknown primary is encountered in 3–8 per cent of cases[2–5]. Of these patients, 45–60 per cent are reported to have lymph node metastases[6–8]. A strong immune response may have been the cause of the disappearance of the primary tumour, without affecting the metastases in lymph nodes or elsewhere Also, the primary tumour may have been overlooked because of its benign appearance or because of its location at a hidden site[9]. The question arises whether patients with an unknown primary, treated for melanoma lymph node metastases, have a different prognosis compared with those with a known and adequately treated primary tumour. It is conceivable that due to an antitumour immune response fewer tumour cells are dissociated from the primary than would normally occur. In such a case the chance that micrometastases are limited to the regional lymph nodes would be high. In order to extract more information concerning the patients with these features the clinicopathological findings and prognosis of those treated at our institute were documented.

Patients and methods

This study concerns a consecutive series of patients with regional lymph node metastases, with or without in transit metastases, from melanoma with an unknown primary tumour site (stage II, according to Union Internationale Contre le Cancer, UICC, directives) treated between 1961 and 1986. All patients had undergone a thorough physical examination including oronasal, anorectal, genital and hair-covered areas. Attempts were made to identify a primary lesion by performing biopsies of suspicious-appearing moles, halo nevi or areas of depigmentation. In determining the final study group patients with the following criteria were excluded[2]: (1) patients who gave a past history of having had a mole, birthmark, freckle, chronic paronychia or skin blemish treated by excision, cauterization or cryotreatment without available microscopical slides of the entire treated lesion for review purposes; (2) patients with a scar of previous local treatment in the skin area draining to the affected lymph node basin, if microscopical slides were not available for review, (3) patients who had undergone orbital enucleation.

The diagnosis of melanoma was established by lymph node biopsy, by needle aspiration with cytological examination or by excision of an in transit metastasis In all patients the histological slides were re-evaluated The number of lymph nodes involved in the dissection specimens was assessed. If additional investigations did not reveal distant metastases, the patients were considered to have stage II disease.

Survival curves were calculated based on the life table method In order to evaluate the role of criteria significantly associated with survival, a multifactorial analysis was carried out by means of a stepwise proportional hazard analysis

The study group consisted of 26 Caucasian patients, 15 men and 11 women, with a follow-up varying from 24 months to 265 months (median 97 months). The age ranged from 21 to 81 years, with a mean of 45 years.

At clinical presentation 21 patients had regional lymph node metastases (stage IIb) and five patients initially presented with in transit metastases and developed regional lymph node metastases (stage IIab) simultaneously or later in the course of the disease. The site of lymph node involvement was inguinal, axillary or cervical in ten, seven and nine patients respectively (*Table 1*). Six patients (23 per cent), one of them with concomitant in transit metastases, had a history of spontaneous regression of a possible primary tumour, 9 months to 4 years before lymph node dissection, the sites being situated in the skin area draining to the affected lymphatic basin. In these patients an excisional biopsy of the depigmented area showed histological features of a melanoma which had undergone complete primary regression

All patients were operated on with curative intent In 25 patients, a radical groin, axillary or neck dissection was performed. In three cases the neck dissection was combined with a superficial parotidectomy. One patient with a preauricular lymph node metastasis underwent a superficial parotidectomy only. In two patients, the lymph node dissection was combined with a normothermic isolation perfusion with L-phenyl-alanine mustard (melphalan) because of (synchronous) in transit metastases in the extremity.

Ten patients (38 per cent) received adjuvant radiation therapy to

Table 1 *Site of lymph node metastases from melanoma with an unknown primary tumour, according to sex*

	Number of patients		
Site	Male	Female	Total
Groin	2	8 (4*, 3†)	10
Axilla	5 (2*, 1†)	2	7
Neck/parotid	8 (1†)	1	9
Total	15	11	26

* Patients with a history of spontaneous regression of a skin lesion; † patients with concomitant in transit metastases

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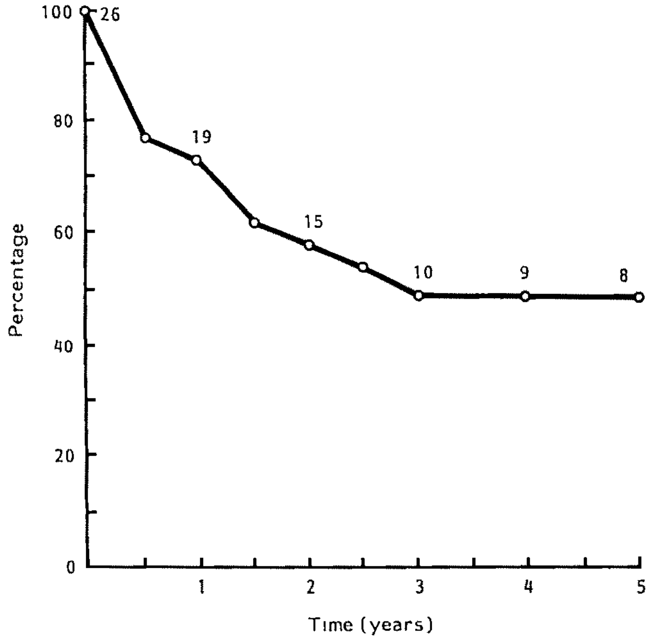

Figure 1 *Survival curve (actuarially calculated) of 26 patients with lymph node metastasis from melanoma with an unknown primary. Numbers indicate number of patients under analysis at that time*

the operative field and the more proximal lymph node area. In 13 out of 22 patients (59 per cent) who had primarily undergone a diagnostic lymph node biopsy, residual melanoma was found in the definitive lymph node dissection specimen.

Results

Following lymph node dissection the overall actuarial survival rate after 1, 2, 5 and 10 years was 73, 58, 49 and 49 per cent respectively (*Figure 1*). The median survival was 35 months. After 1, 2, 3, 4, 5 and 10 years, 19, 15, 10, 9, 8 and 3 patients were still alive. In the patients with tumour recurrence, the disease-free interval after lymph node dissection ranged from 1 to 41 months with a median of 4 months In these patients 78 per cent of the recurrences appeared within 1 year and 92 per cent within 2 years following the node dissection. Single factor analysis revealed the following results. The age of the patients did not affect the prognosis. Females had a better 5-year survival rate than males, 82 per cent and 25 per cent respectively ($P = 0·009$). Difference in survival was found also between patients with cervical lymph node metastases and those with axillary or groin metastases, 5-year survival rates being 11 per cent, 57 per cent and 80 per cent respectively ($P = 0·008$). Comparing patients with and without in transit metastases, 5-year survival rates were not statistically significantly different and were respectively 40 per cent and 51 per cent. Prognosis in the patients who received adjuvant radiation therapy did not differ much from that of the other patients, with a 5-year survival of 40 per cent and 55 per cent respectively. Patients with a history of spontaneous regression of a skin lesion had a 5-year survival rate of 80 per cent compared with 40 per cent in the rest of the group ($P = 0·039$). The 11 patients with only one lymph node involved had a better 5-year survival rate than the patients with more than one lymph node involved, 82 per cent and 27 per cent respectively ($P = 0·006$).

By single factor analysis, sex, spontaneous regression of the primary tumour, site and number of lymph node metastases were found to be significant prognostic factors. However, on regression analysis with survival as end point, only the site of metastases in the neck was found to maintain a significant *P* value, even when corrected for the number of lymph nodes involved ($P = 0·048$), while sex, spontaneous regression and number of lymph nodes involved were no longer significant (*Table 2*).

Discussion

The overall survival rate (49 per cent) in this study group is better than the 5-year survival rate of about 35 per cent which is generally reported in adequately treated stage II melanoma patients with a known primary[10,11] This is in agreement with the results of two other studies concerning lymph node metastases from melanoma with an unknown primary, in which 5-year survival rates of 48 per cent and 58 per cent respectively were described[4,6]. Also, in a previous study on stage II patients with prognostically unfavourable characteristics, the patients with exclusively regional lymph node metastases from 'unknown primaries' were found to be those with the longest survivals[12]. In contrast with these findings, however, there are other reports concerning patients with unknown primaries in which a less favourable 5-year survival rate (respectively 25·5 per cent[2], 29·7 per cent[7] and 33 per cent[13]) was found.

Various explanations have been given for the absence of a primary site in metastatic melanoma. (1) The primary tumour was overlooked because it was too small to be detected, was located in a hair-covered area or had a benign appearance[2,11]. However, in patients with an untreated primary, a long-lasting survival can hardly be expected since the potential for dissemination remains. Moreover, one would expect the primary to become clinically evident at a later stage during the follow-up period[9]. (2) The primary tumour originated from a visceral organ[12]. This supposition is not very likely since the groin, the axilla and the neck would then not be regional node basins. (3) The melanoma arose *de novo* within a node-bearing area, where it possibly derived from malignant changes in benign nevoid cells which are occasionally present in lymph nodes[2,14,15]. The fact, however, that lymph node involvement in unknown primaries is not encountered in other lymph node areas, such as within the abdomen for example, is not in favour of this argument[16]. (4) The occult primary tumour was previously destroyed by a coincidental trauma[16]. Obviously it is very unlikely that a patient would not remember the existence of a former skin lesion which had been destroyed by a (substantial) trauma Moreover, such trauma would be generally expected to leave a scar. (5) The 'occult' primary was located in the skin of the node-bearing area and was removed, unnoticed, during the radical lymph node dissection. This also seems to be a most unlikely occurrence[6] (6) Complete spontaneous regression of the primary lesion occurred[2].

In our series six patients (23 per cent) were found to have a history of spontaneous regression of a skin lesion An even higher incidence might be present as, especially in skin areas which cannot be surveyed easily, spontaneous regression of a pigmented lesion may have escaped the patient's attention. Although melanoma comprises only 1 per cent of all malignancies in the human, 11 per cent of all cases of spontaneous tumour regression are reported to be in melanoma patients[17]. Signs of (partial) regression are seen in 12–16 per cent of cutaneous melanoma cases[18], occurring only in the superficial spreading and lentigo maligna type[18,19]

The clinical appearance of spontaneously regressing melanoma varies greatly[18,20]. The most common finding is a

Table 2 *Prognostic factor analysis concerning survival*

Multifactorial analysis	Step 0, *P* value	Step 1, *P* value*	Step 2, *P* value†
Sex	0·0091	0·154	0·177
Spontaneous regression	0·0390	0·284	0·327
Number of lymph nodes involved	0·0061	0·058	0·058
Site of lymph nodes			
groin	0·0419	0·478	0·714
axilla	0·4496	0·478	0·714
neck	0·0052	0·005	0·048

* Corrected for site (neck); † corrected for number of nodes

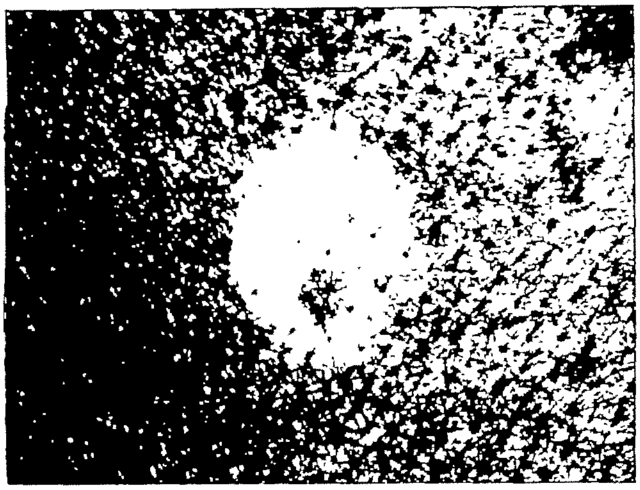

Figure 2 *Vitiligo of the skin after spontaneous regression of a previous pigmented skin lesion*

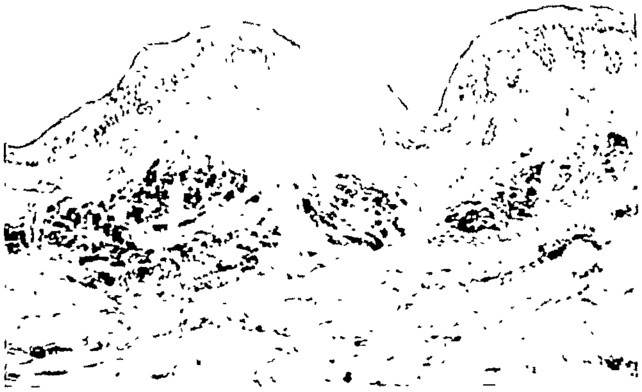

Figure 3 *Histology of a depigmented skin area, fitting with complete regression of a skin melanona, with pigment-laden macrophages in the absence of viable tumour cells*

distinctly bordered depigmented area which correlates with the size of the original lesion (*Figure 2*). Sometimes there are small areas of brown or black pigment within the depigmented area. Microscopically the regression phenomenon is characterized early on by a dense lymphocytic inflammatory infiltrate, followed by disappearance of tumour cells from the epidermis and dermis. Later, fibrosis with the formation of ectatic blood vessels occurs and often a large number of melanophages (*Figure 3*) are present[18,21]

The prognostic significance of spontaneous regression remains a subject of dispute[22]. In the present study the six patients with a history of complete spontaneous regression of a possible primary tumour, as compared with those without this history, fared better, although no statistical significance was reached In other series both groups were reported to have similar survival rates[3,13] Many speculations have been made regarding the mechanism of spontaneous regression[23–27] Some have suggested that immunological factors might be responsible for regression of the primary tumour, but with the occurrence of metastases the level of antitumour immunity falls[23]. Others assumed a pattern of selectivity, so that certain cell clones are killed while, in metastases, others lacking expression of relevant antigens are not[24]. In metastases, as compared with the primary tumour, a decreased expression of certain antigens has been observed[25]

Although in the present study only the site of metastases in the neck had a significant, unfavourable, influence on survival on regression analysis, the relatively small number of patients may be a limitation. In a larger study it may be possible to detect significant differences for additional factors such as sex or the number of lymph nodes involved. Single factor analysis of our data revealed that the prognosis for females was more favourable than for males. In female stage I melanoma patients a better prognosis is well documented, however, this sex difference is not found in stage II patients with a known primary tumour[28] In the present series this difference did not show up in the multifactorial regression analysis because most of the female patients had lymph node metastases situated in the groin, as opposed to the male patients in whom the metastases were mainly situated in the neck. In the patients with neck metastases the prognosis was significantly worse than in those with inguinal or axillary metastases, by multifactorial analysis A reason for this last finding might be that in some of these patients the primary tumour was situated on the scalp and therefore was not discovered.

Apart from the characteristics of the primary tumour, the prognosis in stage II melanoma patients with a known primary tumour is reported also to depend on the number of positive lymph nodes[10,11] In the present study this finding could only be substantiated at single factor analysis.

According to the literature, in a substantial number of patients in whom a diagnostic biopsy of palpable nodes was performed residual melanoma was found in the specimen of the complementary radical lymph node dissection[6,29]. Since metastases are capable of dissemination, just like primary tumours, it is likely that melanoma patients with regional lymph node metastases from an unknown primary benefit from similar surgical treatment as those with a known primary Radical node dissection is, therefore, advocated in these patients

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Postoperative management of patients with total exocrine pancreatic insufficiency

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The occurrence of maldigestion and malnutrition was studied in 14 patients who had undergone pancreaticoduodenectomy and occlusion of the Wirsung duct with Neoprene®. Before discharge patients were put on a 70 g/day dietary fat intake. Mean faecal fat excretion was 32·9 g/day without enzyme replacement and fell to 14·2 g/day with pancrelipase supplementation. At discharge all patients were underweight (88 per cent of the usual mean body-weight) and nine patients showed alteration in laboratory nutritional parameters. At the time of discharge a low-fat diet (50 g/day) was prescribed. Six months after surgery, mean faecal fat excretion decreased further to 8·3 g/day ($P<0.01$) *and all patients but one gained weight, reaching 93 per cent of the usual mean body-weight with normalized nutritional parameters. Our data show that the combination of enzyme replacement therapy and low-fat diet allows good correction of steatorrhoea and a significant improvement in nutritional status.*

Keywords: Pancreaticoduodenectomy, pancreatic enzymes, nutritional status, steatorrhoea

The exocrine pancreatic insufficiency which often develops after pancreaticoduodenectomy is usually well corrected by enzyme supplements, so that these patients do not experience maldigestion and malnutrition[1–3]. The picture is quite different in patients undergoing total pancreatectomy in whom malnutrition often occurs despite enzyme replacement[4–7]. This can be due to inadequate correction of maldigestion in these patients with total pancreatic insufficiency or to the presence of a brittle postsurgical diabetes which could contribute to malnutrition, or both.

The ability of enzyme supplements to correct maldigestion and thus prevent malnutrition after surgical suppression of exocrine pancreatic function can be well investigated in patients who retain endocrine function. In this respect, subjects undergoing pancreaticoduodenectomy associated with Neoprene® (Du Pont de Nemours and Company, Wilmington, Delaware, USA) injection into the residual pancreatic stump are unique. Neoprene is a synthetic glue able to suppress exocrine pancreatic secretion by inducing progressive fibrosis of the acinar tissue, but sparing the insular component[8,9]. In a previous series of patients we were able to improve postoperative nutritional status, but could not completely correct steatorrhoea by using pancrelipase enteric-coated microspheres while patients were kept on a diet containing 70 g/day of lipids[10].

In the present study we evaluated the possibility of normalizing faecal fat excretion while maintaining the nutritional gain by combining a low-fat diet (50 g fat/day) with enzyme replacement

Patients and methods

Between January 1986 and March 1988, 20 patients underwent pancreaticoduodenectomy (Whipple procedure) with injection of Neoprene latex into the duct of Wirsung, as previously described by Di Carlo *et al.*[9]. Gastric resection was limited to antrectomy without vagotomy. Reconstruction was achieved by end-to-side hepaticojejunostomy and by gastrojejunostomy using the first jejunal loop. The pancreatic stump was left disconnected from the alimentary canal. Five patients with cancer had recurrence within 6 months of operation, and were not considered fit for this study, since the persistence of neoplasia could cause malnutrition, regardless of the presence of maldigestion/malabsorption. One patient was lost to follow-up. The 14 remaining patients (11 men and three women), mean age 55 years (range 23–77 years) were included in the study. For these patients the indication for pancreaticoduodenectomy had been chronic pancreatitis (four cases), pancreatic carcinoma (four cases), cancer of the papilla of Vater (three cases) or an endocrine pancreatic tumour (three cases). None of these patients had preoperative diabetes.

Starting 5 days before discharge (which occurred 18·2(4·7) days (mean(s.d.)) after surgery), patients were put on a diet of 2400 kcal/day, with a fat intake of 70 g/day as in previous series[9,10]. During the first 2 days, patients were off enzyme supplement therapy; from the third day onwards, patients were treated with pancrelipase enteric-coated microspheres (ECM) (16050 United States Pharmacopoeia (USP) units of lipase per meal, equivalent to three capsules of Pancrease®, Cilag S.p.A., Milan, Italy). All patients were treated with ranitidine (150 mg twice daily) as part of the routine postoperative management. Throughout this 5-day period, faecal fat excretion was measured daily by the method of Van de Kamer *et al.*[11] (a daily excretion of less than 7 g/day was considered as normal). The stool weight and the number of bowel movements were also recorded daily. While patients were off enzyme supplementation the D-xylose tolerance test was carried out by the Roe and Rice technique[12] to rule out bacterial overgrowth, small bowel mucosal changes and shortened intestinal transit time as concomitant causes of malabsorption. At time of discharge, serum albumin (normal value >35 g/l), total iron binding capacity (normal value >45 μmol/l), total lymphocyte count (normal value $>1500\times10^6$/l) and serum cholinesterase activity (normal value >2500 units/l) were tested as indicators of nutritional status. Patients were then advised to follow a regular enzyme supplementation regimen with pancrelipase ECM (16050 USP units of lipase per meal). A diet of 2400 kcal/day with a low fat intake (50 g/day) was also prescribed. Clinical and nutritional follow-up was performed monthly. This included a physical examination, a check on the adequacy of food intake and an assessment of body-weight. Usual body-weight was taken as the pre-illness body-weight in patients with malignancy. In the four patients with chronic pancreatitis, usual body-weight was defined as the body-weight achieved by patients between relapses of the disease. In all patients, ideal body-weight was also calculated according to Davidson[13]. A check on blood chemistry was performed quarterly.

Six months after surgery a nutritional assessment was carried out in all patients, including measurement of nutritional parameters and body-weight. In ten patients faecal fat excretion was measured while they were on a low-fat diet. Blood glucose concentration was measured after overnight fasting and 2 hours after a standard meal. At this time, none of the patients with neoplasia had any clinical evidence of local or systemic recurrence.

The statistical analysis of results was carried out by the Wilcoxon signed-rank test.

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Table 1 *Faecal fat excretion (g/day) in 14 patients after pancreaticoduodenectomy*

Indication for pancreaticoduodenectomy	Dietary fat intake (g/day) 70		50
	Pancreliрase intake* nil	Pancrelipase intake* 16 050	Pancrelipase intake* 16 050
1 Cancer head pancreas	28·8	10·9	7·7
2 Cancer papilla	29·4	14·1	10·5
3 Cancer head pancreas	33·8	19·7	–
4 Insulinoma	45·1	29·1	18·3
5 Chronic pancreatitis	25·6	8·5	5·7
6 Cancer papilla	36·8	9·2	9·1
7 Carcinoid	40·5	21·0	–
8 Chronic pancreatitis	21·1	9·2	5·8
9 Cancer head pancreas	15·9	5·9	5·4
10 Carcinoid	31·9	19·1	8·9
11 Cancer papilla	36·1	9·3	5·3
12 Chronic pancreatitis	39·3	18·5	–
13 Cancer head pancreas	39·0	8·8	6·3
14 Chronic pancreatitis	37·4	15·6	–
Overall mean	32·9^a	14·2^b	
Standard deviation	8·1	6·6	
Mean of 10 patients who also had studies while on low fat intake	30·9^c	12·4^d	8·3^e
Standard deviation	8·7	6·9	3·9

* United States Pharmacopoeia units of lipase per meal. **a** *versus* **b** and **c** *versus* **d**, $P<0·001$; **d** *versus* **e**, $P<0·01$. *P* values obtained using Wilcoxon signed-rank test

Table 2 *Influence of low-fat diet and enzyme replacement therapy on nutritional parameters*

Nutritional parameter	Before discharge (mean(s.d.))	6 months after surgery (mean(s.d.))	*P**
Serum albumin (g/l)	36·0(6·0)	43·5(5·0)	<0·01
Total iron binding capacity (μmol/l)	47·2(9·3)	57·3(10·9)	<0·01
Total lymphocyte count (10^6/l)	1934(776)	2651(839)	<0·001
Serum cholinesterase (units/l)	3453(769)	5181(1293)	<0·001

* *P* values obtained using Wilcoxon signed-rank test

Results

The D-xylose tolerance test was evaluated when patients were off enzyme supplementation and was normal in all cases. All patients showed marked steatorrhoea when they were off enzyme supplementation and on a diet of 70 g/day of fat. In all patients, pancrelipase ECM supplementation allowed a reduction of faecal fat excretion, but excretion became normal in only one case (*Table 1*). The corresponding mean values of stool weight were 433(127) g/day (mean(s.d.)) when patients were off enzyme supplementation and 215(92) g/day when patients were on pancrelipase ECM ($P<0·001$). The average number of bowel movements was 1·5 per day when patients were on enzyme supplements.

At discharge, all patients were underweight with respect to their usual body-weight (mean weight 88·3 per cent of usual body-weight). Nine patients showed an alteration in at least one nutritional indicator Moreover, in three patients a concomitant alteration of three nutritional parameters was observed. Nutritional status was re-evaluated in all patients 6 months after operation, while they were on a low-fat diet. The average values of nutritional indicators showed a significant increase after 6 months of enzyme replacement therapy (*Table 2*). Individual variations in nutritional indicators are shown in *Figure 1a* and *b*. Six months after surgery, all but one patient showed normal values of nutritional parameters. *Table 3* shows the changes in body-weight with time. After 6 months of pancrelipase ECM, 13 patients gained weight, reaching a mean of 93 per cent of their usual body-weight (average increase 3 kg), and six of 14 patients reached their usual body-weight. Moreover, 6 months after surgery all patients who had shown a marked weight loss before hospitalization exceeded their preoperative body-weight.

The values of faecal fat excretion measured 6 months after surgery in ten patients, while they were on pancrelipase ECM supplementation and a low-fat diet, are also reported in *Table 1*.

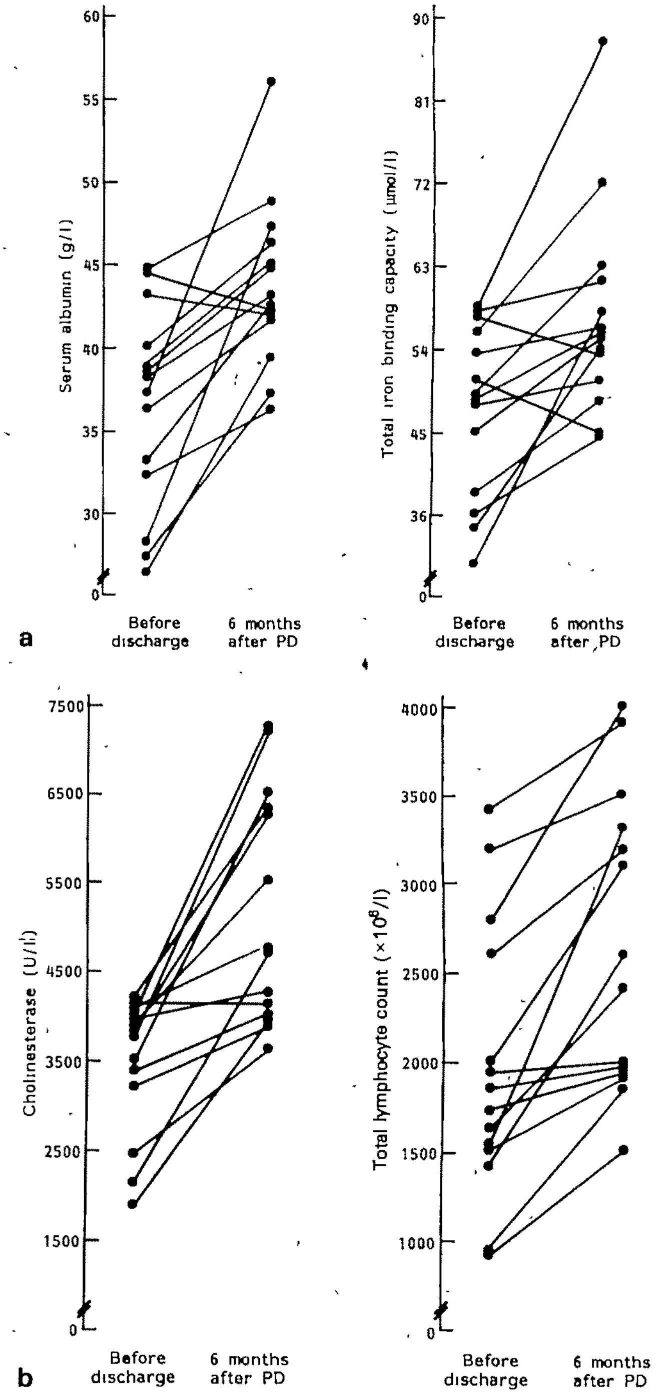

Figure 1 **a** *Individual variations in serum albumin and total iron binding capacity before discharge and at 6 months after pancreaticoduodenectomy (PD).* **b** *Individual variations in serum cholinesterase and total lymphocyte count before discharge and at 6 months after pancreaticoduodenectomy*

Table 3 *Patients' body-weight before and after pancreaticoduodenectomy*

Patient no.	Ideal body-weight (kg)	Usual body-weight (kg)	Admission weight (kg)	Weight before discharge (kg)	Weight at 6th postoperative month (kg)
1	81	87	78	76	87
2	67	69	69	67	69
3	54	56	54	54	56
4	54	51	51	50	51
5	68	63	59	60	63
6	61	60	56	54	60
7	53	50	46	45	49
8	73	72	65	67	67
9	67	80	72	70	74
10	55	56	50	50	51
11	56	60	53	53	54
12	58	56	46	44	50
13	61	60	49	50	51
14	69	65	42	44	46
Mean	62·6	63·2	56·4	56·0	59·1
Standard deviation	8·4	10·6	10·8	10·3	11·6
Percentage of usual body-weight					
Mean	99·7	100	89·4	88·6	93·3
Standard deviation	6·7	0	8·8	8·0	8·4
			$P<0·01$*		$P<0·01$*

* *P* values obtained using the Wilcoxon signed-rank test

Five of these patients had a faecal fat excretion within the normal range. In addition to a significant reduction in faecal fat excretion, the low-fat diet allowed an increase in mean body-weight from 59·7(9·6) to 62·7(11·9) ($P<0·01$). The mean value of stool weight observed in these ten patients 6 months after surgery was 124(62) g/day. The average number of bowel movements in the 6-month period after operation, when patients were on low fat diet, was 0·96 per day. Fasting and postprandial blood glucose 6 months after pancreaticoduodenectomy was still within the normal range in all patients.

All patients had good compliance with pancrelipase ECM.

Discussion

Exocrine pancreatic insufficiency after pancreaticoduodenectomy has been reported by several authors with the incidence[1–3] varying according to the criteria used to evaluate the data. Howard[1] reported that it occurred in about 40 per cent of the patients. Fish *et al.*[2] reported that half of their 49 patients were unable to regain their weight or resume their previous occupations; all patients had an increased stool frequency (three to 12 stools/day). Faecal fat excretion was measured in six of these patients and five of them had steatorrhoea; after enzyme replacement, faecal fat excretion returned to within the normal range in all patients. Mori *et al.*[3] observed slight steatorrhoea in all six of their patients while they were off enzyme supplementation therapy. This exocrine pancreatic insufficiency can also be attributed to causes such as a reduction in pancreatic mass, postoperative pancreatitis and to obstruction or stenosis of the pancreaticojejunal anastomosis which results in the atrophy of the residual acinar tissue. However, in the experience of several authors[1–3] exocrine pancreatic insufficiency after pancreaticoduodenectomy is usually well corrected by adequate enzyme supplementation therapy.

Greater difficulties are encountered in correcting maldigestion due to total loss of exocrine pancreatic function. Braasch *et al.*[4] were unable to control steatorrhoea in two of 14 patients after total pancreatectomy despite increasing doses of enzyme supplements. Cooper *et al.*[14] who reported 83 patients after total pancreatectomy found poor correction of exocrine pancreatic insufficiency in 21 patients. These studies recognized the development of malnutrition secondary to maldigestion and/or malabsorption in a considerable portion of total pancreatectomy patients despite correct enzyme replacement. In this respect, the brittle diabetes associated with total pancreatectomy is thought to compound the nutritional impairment of these patients. Thus, the true impact of complete loss of exocrine pancreatic function on nutritional status can be better evaluated in patients who maintain endocrine pancreatic function. Previous studies have demonstrated that pancreaticoduodenectomy with Neoprene injection into the duct of Wirsung suppresses exocrine pancreatic secretion, but does not impair endocrine function[8,15,16]. In our experience fasting blood glucose levels remained within the normal range up to 3 years after pancreaticoduodenectomy with Neoprene injection and no variation was observed in insulin and glucagon responses to oral glucose and intravenous arginine infusion[9].

In a previous series of such patients, enzyme supplementation therapy (16050 USP units of lipase per meal) improved nutritional status, but only partially corrected steatorrhoea while patients received a diet of 70 g/day of fat[10]. This could be simply attributed to an insufficient amount of enzyme supplements[17]; however, higher enzyme intake would require administration of a very large number of capsules with a consequent reduction in patient compliance. Alternatively, isocaloric substitution of part of the dietary fat intake might allow complete control of steatorrhoea in these patients.

In the present series of patients with pancreaticoduodenectomy and pancreatic duct occlusion we demonstrated that a low-fat diet (50 g/day) combined with the supplementation of 16050 USP units of lipase per meal can almost correct the steatorrhoea while maintaining a good nutritional status. In the early postoperative period, enzyme supplementation combined with a normal fat diet (70 g/day) did not allow complete control of steatorrhoea, and resulted in a fractional fat absorption (79·9 per cent), similar to that of patients with advanced chronic pancreatitis having the same implemental therapy[18–21]. It is worth noting that in all of these patients the postoperative D-xylose test was normal which allows us to invoke maldigestion as the main cause of faecal loss.

Over the 6 months of the study patients appeared to accept and strictly follow the 2400 kcal/day diet and tolerate the enzymatic supplementation therapy without difficulty. This was achieved by strict nutritional follow-up especially in the early postoperative period.

In ten patients we re-evaluated faecal fat excretion 6 months after operation The mean value of faecal fat excretion was 8·3 g/day, with five of ten patients having excretion within the normal range. The mean coefficient of fat absorption rose to

83·4 per cent. This indicates that a smaller proportion of the ingested fat is not absorbed when the dietary fat load is decreased.

The weight gain which occurred in these patients during this period provides good evidence that the caloric intake of the patients while at home was adequate, and that the reduction of faecal fat excretion is not related to insufficient food intake. Thus, it appears that isocaloric substitution of dietary fat with carbohydrates or proteins can improve the absorption of food and the nutritional status of these patients.

The association of enzyme replacement therapy and a low-fat diet allowed significant improvement of nutritional status in our patients who also regained their working capabilities Six months after surgery patients reached a mean of 93 per cent of their usual body-weight and it must be emphasized that six of them reached their usual body-weight. This is particularly meaningful since most of these patients showed a marked preoperative weight loss because of their disease. It is also worthy of note that only one of the four patients with chronic pancreatitis, who certainly became teetotal, reached the usual body-weight. The other three patients only partially recovered from the preoperative weight loss, reaching a mean of 83 per cent of their usual body-weight; one of them certainly continued to drink and we are uncertain about the true alcohol consumption of the other two

In conclusion, our data show that steatorrhoea can be corrected in patients totally devoid of exocrine pancreatic function by combining a low-fat diet (50 g/day of fat) with enzyme replacement. This allows an improvement in nutritional status and recovery of a good quality of life.

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Outcome of surgery for non-palpable mammographic abnormalities

Four hundred and ninety-three women underwent 515 localization biopsies for non-palpable mammographic abnormalities. The mammographic abnormality was located with a hooked wire in 509 cases. Specimen radiology was performed on all excised tissue. The mammographic abnormality was visualized in the first piece of tissue excised in 402 (78·1 per cent) cases and complete excision was achieved in 476 (92·4 per cent). A palpable nodule was removed in 38 (7·4 per cent) cases and in 17 (44·7 per cent) was shown to contain a carcinoma. The mammographic abnormality was missed in 14 (2·7 per cent) cases or only partly excised in 13 (2·5 per cent). Overall 144 (28·0 per cent) localization biopsies were malignant. The mammographic abnormality was not visualized on the specimen radiograph more frequently in women aged under 55 years, in women with dense breast (Wolfe grade DM or DY) or in those whose mammographic abnormality contained only microcalcification. The 27 women in whom the mammographic abnormality was not visible on the specimen radiograph underwent repeat mammography 2 months later. Only two women required a further localization biopsy and the mammographic abnormality was recovered in the first piece of tissue excised. Women with a carcinoma underwent mastectomy or wide local excision, and residual carcinoma at the localization biopsy site was found in 64 (44·4 per cent) cases. Oestrogen receptor analysis by ligand binding assay was possible in only 71 (49·3 per cent) carcinomas. If the specimen radiograph does not show the mammographic abnormality within pieces of tissue excised and there is no palpable nodule it may be best to conclude the biopsy. In this series these missed lesions were usually benign. Only rarely is a second localization biopsy required and this is performed without difficulty.

Keywords: Breast, biopsy, mammography, non-palpable

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Edinburgh was one of two screening centres established in 1980 to offer mammography as part of the UK Trial of Early Detection of Breast Cancer[1,2]. In Edinburgh mammography is also performed on women aged 35 years or over attending the symptomatic breast clinic. Women from either source found to have a suspicious non-palpable mammographic abnormality requiring localization biopsy were referred to the University Department of Surgery Breast Unit[3,4]. This paper reviews that experience.

Patients and methods

The folders and mammograms of women who underwent a localization biopsy for non-palpable mammographic abnormalities between November 1976 and December 1987 in the University Department of Surgery Breast Unit were reviewed. At the initial visit the history and clinical findings were prospectively recorded on special proformas In addition a structured hospital clerking sheet was completed at the time of admission These records were used to compile a computer database that included the source of referral, the age at biopsy, the presence of symptoms and the number of previous mammograms Operative details (including the result of the specimen radiograph) were taken from the operation notes dictated immediately after surgery The histopathological diagnosis was checked by reference to a separate register held in the Department of Pathology[1,2]

The mammograms were reviewed by a single radiologist (H L.MacD) who was unaware of the clinical history, the examination findings or the histopathological diagnosis. The mammographic abnormality was classified on a standard form including 15 characteristics, and the breast parenchymal pattern was graded (Wolfe classification[5] modified by Roebuck[6])

The localization biopsy was performed using a guide-wire as described by Frank *et al* [7] although different techniques and hooked wires were assessed during the study period After placement of the wire its relationship to the abnormality was immediately confirmed by check mammogram. Under general anaesthesia an incision was made in the breast in a manner that would not prejudice a future cancer operation, the wire was identified and traced towards its tip, and the relevant tissue was excised The excised specimen was radiographed in the theatre suite (Faxitron model 43805N, Hewlett Packard, Palo Alto, California, USA) and if shown to contain the abnormality the operation was concluded

If the radiograph did not show the abnormality, further tissue was excised and submitted for specimen radiology A palpable nodule was sometimes evident during the operation, and this was excised and radiographed If the mammographic abnormality was not identified on successive pieces of tissue the operation was concluded. These women underwent mammography 2 months later and if necessary a second localization biopsy was performed

Results

A total of 515 mammographic abnormalities were excised from 493 women. In all but six cases the needle localization technique we have previously described was used (*Table 1*)[4] Five superficial abnormalities were localized using a cutaneous lead marker and in one early case the 'double dye' technique was

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This paper formed the basis of a presentation to the Association of Surgeons of Great Britain and Ireland in Edinburgh on 30 March 1989.

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Table 1 *Localization biopsies in 493 women*

Procedure	No. of women	No. of biopsies
Single localization biopsy	465	465
Two localizations at the same time	12	24
Two localizations at a different time	8	16
Skin marker	5	5
'Double dye' technique	1	1
Second localization because mammographic abnormality was missed on the first occasion	2	4
Total	493	515

Table 2 *Pathology of 515 non-palpable mammographic abnormalities*

	n
Benign	
Normal	35 (6·8)
Fibrocytic disease	
Non-proliferative	75 (14·6)
Proliferative	59 (11·5)
Atypical	38 (7·4)
Fibroadenoma	54 (10·5)
Cysts	19 (3·7)
Duct ectasia	18 (3·5)
Sclerosing lesions	26 (5·0)
Other	47 (9·1)
Total benign	371 (72·0)
Malignant	
In situ carcinoma	
Lobular	5 (1·0)
Ductal	43 (8·3)
Mixed	2 (0·4)
Total *in situ*	50 (9·7)
Microinvasive	16 (3·1)
Invasive carcinoma	
Special type	17 (3·3)
No special type	60 (11·7)
Cystosarcoma phyllodes	1 (0·2)
Total invasive	94 (18·3)

Values in parentheses are percentages

used[8]. There were no operative details in 12 (2·3 per cent) folders. There was no mortality and the complication rate was low (infection 5 (1·0 per cent); haematoma 10 (1·9 per cent)). The histopathology of the excised lesions is given in *Table 2*; overall 144 (28·0 per cent) lesions were malignant giving a benign:malignant ratio of 2·6:1.

Complete excision of the mammographic abnormality was confirmed by specimen radiography in 476 (92·4 per cent) localization biopsies (*Table 3*). In 402 (78·1 per cent) cases the specimen radiograph confirmed that the first piece of excised tissue contained the mammographic abnormality; this included the six women in whom the needle localization technique was not used. The mammographic abnormality was in the second or third piece of tissue submitted for specimen radiology in 29 (5·6 per cent) and seven (1·4 per cent) biopsies respectively. Any palpable nodules found during biopsy were excised and radiographed; 38 (7·4 per cent) nodules contained the mammographic abnormality and 17 (44·7 per cent) were malignant.

Twenty-seven (5·2 per cent) localization biopsies were concluded without radiological confirmation that the mammographic abnormality had been fully excised (*Table 3*). Despite excision and specimen radiography of several pieces of breast, the mammographic abnormality was not identified in 14 (2·7 per cent) cases and only part of the abnormality was identified in 13 (2·5 per cent) cases. Two of the lesions partly excised were malignant.

The 476 patients in whom the lesion was completely identified on the specimen radiograph were compared with the 27 patients in whom it was not completely identified (*Table 4*). The mean(s.d.) age of women at the breast clinic tended to be less than that of women at the Edinburgh Breast Screening Clinic (49·9(7·1) *versus* 53·8(8·5) respectively; Student's *t* test, t=2·31, P=0·021). The mammographic abnormality was less likely to be retrieved if the histopathology was benign, if the woman was under 55 years of age, if she had dense breasts or if the mammographic abnormality contained only microcalcification. Although these differences were significant there was great disparity in the size of the two groups. Two of the 27 mammographic abnormalities not visualized on the specimen radiograph were malignant but as both had been partially excised the diagnosis of cancer had been established.

Repeat mammography was performed 2 months after the localization biopsy if the specimen radiograph did not confirm complete removal of the mammographic abnormality or if histopathological evaluation revealed only normal breast tissue despite the mammographic abnormality being identified on the specimen radiograph. In two women the mammographic abnormality was still suspicious of malignancy and the localization biopsy was repeated. The localization was completed without difficulty using a guide-wire and the specimen radiograph confirmed that the first piece of tissue excised contained the abnormality. Both had benign histopathology.

If the localization biopsy demonstrated a malignancy the woman routinely underwent either mastectomy or wide local excision of the biopsy site. The localization biopsy site was routinely examined for evidence of residual carcinoma. This was found in 64 (44·4 per cent) specimens (*Table 5*). Invasive carcinomas were more frequently completely excised than carcinoma *in situ* (χ^2=8·278, one d.f., P=0·0004). It is our routine practice to submit all tissue suspicious for malignancy for oestrogen receptor ligand assay. There was insufficient tissue for the assay in 71 (49·3 per cent) carcinomas.

Discussion

The technique of localization biopsy used in our unit has been previously described[3,4]. The results presented in this paper demonstrate that our technique is satisfactory and that the mammographic abnormality can be removed in over 90 per cent of localization biopsies. This has been achieved in a specialized breast unit where the radiology suite is adjacent to the operating

Table 3 *Number of attempts required to excise the mammographic abnormality*

	Malignant	Benign	Total
Abnormality identified in specimen radiograph			
First attempt	112	284	396
Second attempt	8	21	29
Three or more attempts required	0	7	7
Within a clinical nodule (more than one excision)	17	21	38
Skin marker/double dye (all removed in first excision)	1	5	6
Subtotal	138	338	476
Abnormality not identified in specimen radiograph			
Partial excision only	2	11	13
Abnormality not on specimen radiograph	0	14	14
Subtotal	2	25	27
No note of operation	4	8	12
Total	144	371	515

Table 4 *Characteristics of the mammographic abnormalities not fully identified on the specimen radiograph*

	Mammographic abnormality				
	Visible on specimen radiograph	Not visible on specimen radiograph	χ^2	d.f.	*P*
Malignant	138 (29·0)	2 (7·4)			
Benign	338 (71·0)	25 (93·6)	5·926	1	0·0149
Wolfe pattern					
N1	56 (11·8)	1 (3·7)			
P1	68 (14·3)	1 (3·7)			
P2	72 (15·1)	8 (29·6)			
DS	58 (12·2)	1 (3·7)			
DM	30 (6·3)	2 (7·4)			
DY	105 (22·0)	11 (40·7)	11·37	5	0·0445
Mammographic abnormality					
Microcalcification	205 (43·0)	18 (66·7)			
Parenchymal disturbance	129 (27·1)	6 (22·2)			
Mixed	55 (11·6)	0 (–)	5·94	2	0·0514
No mammogram available	87 (18·2)	3 (11·1)			
No operative note	12 (25)	–			

Values in parentheses are percentages

Table 5 *The completeness of carcinoma excision*

	Complete excision	Incomplete excision	Total
Carcinoma *in situ*	14 (31·1)	31 (68·9)	45
Invasive	41 (58·6)	29 (41·4)	70
Microinvasive	7 (50·0)	7 (50·0)	14
Cystosarcoma phyllodes	1		1
No residual tissue examined			13
No further excision			1
Total			144

Values in parentheses are percentages

theatre, which facilitates close liaison between the surgeon and the radiologist[9].

In this study difficulties in retrieving the mammographic abnormality occurred when the mammographic abnormality contained only microcalcification, in women aged under 55 years and in women with dense breasts (Wolfe grade DM and DY). Usually these lesions were not malignant. It has been suggested that areas of architectural disturbance are not seen on the specimen radiograph because they lose their form when no longer supported by the surrounding breast tissue. This support may be mimicked if the excised specimen is floated in water[10,11]. In this study, however, the majority of 'missed' localization biopsies were those containing microcalcification. It is important that the surgeon excises and radiographs any nodules discovered during the operation: in this study 17 of 38 (44·7 per cent) nodules were malignant.

The placement of the guide-wire has not caused any problems. In the early part of the study the wire was inserted without compression of the breast and the incision was placed adjacent to the wire. The breast is now routinely compressed and the incision normally lies some distance from the guide-wire[12]. Even if the mammographic abnormality does not lie at the tip of the wire or has not been exactly transected, careful examination of the check mammogram will normally guide the surgeon to the relevant piece of tissue.

Specimen radiography is essential during localization biopsy[13,14] and all excised tissue must be radiographed. If, after a second attempt, the mammographic abnormality has not been identified on the specimen radiograph and there is no palpable nodule it is probably best to desist from excising additional tissue If such a policy had been adopted in this series the 27 instances in which the operation was concluded without the mammographic abnormality being visualized on the specimen radiograph would have been increased to 34. None of the additional seven cases had a carcinoma. If the mammographic abnormality was not fully excised or the histopathology revealed only normal breast, a repeat mammogram must be performed 3 months later. It was considered necessary for only two women to undergo a second biopsy, and a benign lesion was retrieved at the first attempt in each.

Only a small quantity of tissue is removed during a localization biopsy and the histopathologist must have priority for examination of the excised tissue. Often there is insufficient tissue for oestrogen receptor analysis. The initial biopsy is often the only opportunity to obtain tissue for oestrogen receptor assay and the present development of cytohistochemical[15] and immunohistochemical assays[16] will overcome this problem.

Women with non-palpable carcinomas are obvious candidates for breast conservation surgery[17,18] but localization biopsy is only a diagnostic procedure. In this study there was residual tumour in 64 (44·4 per cent) of those with a carcinoma and this was more frequent with carcinoma *in situ*. Wobbes *et al.* examined the localization biopsy site of 30 localization procedures with ductal carcinoma *in situ* and found residual tumour in 77 per cent[19]. At present we routinely re-excise the localization biopsy site or perform a mastectomy.

In future fine needle aspiration cytology of non-palpable mammographic abnormalities[20] should increase the proportion of malignant localization biopsies. If a malignant aspirate is obtained the woman can be counselled and the only operation will be the definitive cancer operation Conversely, it may be appropriate to defer the women for review after 6–12 months if a mammographic abnormality that appears to be benign is supported by a benign cellular aspirate

In conclusion, non-palpable mammographic abnormalities are normally excised without difficulty but if not identified after two pieces of tissue, and if any palpable nodules have been excised and radiographed, it may be preferable to discontinue the localization biopsy. A repeat mammogram should be performed 3 months later. Only rarely will it be necessary to undertake a second localization biopsy

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Announcement

Royal College of Surgeons of England

Surgical trainees and prospective candidates are asked to note that, from September 1990, changes will occur in the regulations, content and format of the FRCS (Eng.) examination.

This will now comprise an Applied Basic Science section and a Clinical Surgery-in-General section. The two sections may be taken together or candidates may elect to sit the Applied Basic Science section separately before attempting Clinical Surgery-in-General. The written papers for both sections will be held on the same day The features of the new examination may be briefly summarized as follows:

Applied Basic Science

Candidates must hold a qualification recognized by the General Medical Council as fully Registrable or providing eligibility for Limited Registration in the United Kingdom, and must have completed at least one year of post-Registration experience.

The Applied Basic Science section consists of one three-hour multiple choice question paper comprising 30 questions each in anatomy, physiology, biochemistry and pharmacology, and pathology; and three 20-minute orals in the above three subjects.

Clinical Surgery-in-General

Candidates may enter this section after passing or being exempted from the Applied Basic Science section, having been engaged in acquiring professional knowledge for at least four years since obtaining a recognized qualification (or for three years after UK Full Registration), having completed two years of mandatory training in hospital posts in the British Isles or overseas recognized as suitable training by the College, together with an elective year of experience.

This section consists of a three-hour paper (two hours of short answers and a one hour essay); a clinical comprising long and short cases; and two 20-minute vivas on the principles of operative surgery and postoperative management.

Entry to the oral and clinical parts of both sections will depend upon achieving adequate paper marks. Log books will be required for the Surgery-in-General vivas

Further details about this examination and the FRCS (Eng.) with Otolaryngology together with log books may be obtained from the Examinations Secretary, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK.

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Decreased morbidity and mortality rates in surgical patients with hepatocellular carcinoma

From September 1981 to December 1988, 163 patients underwent hepatic resection for hepatocellular carcinoma. The patients were divided into two groups: those operated on from September 1981 to March 1985 $(n = 58)$ *and those operated on from April 1985 to December 1988* $(n = 105)$. *There was an increase in the number of relatively small hepatocellular carcinomas in 1987–88. Differences in the incidence of accompanying liver cirrhosis (72* versus *62 per cent) were not statistically significant; however, values of the indocyanine green test (21·5* versus *17·0 per cent,* $P < 0{\cdot}01$*) aided in strict patient selection. In more recent years, initial hepatic hilar dissection for control of vascular structures was undertaken and an ultrasonic dissector was used in about three-quarters of these patients. Consequently, the mean estimated blood loss (2500* versus *1300 ml,* $P < 0{\cdot}001$*) and mean intraoperative blood replacement (2200* versus *560 ml,* $P < 0{\cdot}001$*) were significantly less than in the earlier period. Among the 58 patients treated in the early period, hospital morbidity and mortality rates were 52 and 29 per cent respectively. In contrast, the rates were 23·8 and 1·9 per cent respectively among the 105 patients operated on during the recent period* ($P < 0{\cdot}01$). *The decline in hospital mortality is attributed to the careful selection of patients, use of modern tools, and a diminished blood loss.*

Keywords: Hepatocellular carcinoma, hepatic resection, blood transfusion, hospital mortality, hospital cost

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The occurrence of postoperative complications following hepatic resection remains a problem and can result in hepatic failure and death. The mortality rates after hepatectomy reported in the early 1980s, both in Eastern and Western countries, were over 20 per cent[1,2]. To determine the functional reserve of the liver, we routinely make use of serial measurements of serum lecithin cholesterol acyltransferase activity[3], portal pressure[4], and/or the indocyanine green test[5], all of which aid in predicting postoperative hepatic failure. We have also used plasma exchange therapy in patients with progressive hepatic failure, which has a high mortality rate[6]. Other factors which may have influenced outcome include the intrasplenic administration of OK-432 (an immunostimulant derived from *Streptococcus* species and successfully used to treat hepatic failure in rats[7]) and mechanical ventilation[8] in some patients. In cases of surgery for hepatocellular carcinoma, postoperative recurrence remains a problem[9,10]. However, the latest mortality rates after hepatectomy are now less than 10 per cent[11,12]. In our clinics the mortality rates have also decreased. We describe here our 1981–88 experience with 163 hepatic resections performed for hepatocellular carcinoma.

Patients and methods

In September 1981, intraoperative ultrasonography for liver surgery was introduced in our clinics. From this time to December 1988, 163 Japanese patients underwent hepatic resection for hepatocellular carcinoma at the Second Department of Surgery, Kyushu University Hospital. There were 136 men and 27 women. The mean age was 56·3 years, ranging from 33 to 76 years. One hundred and seven patients (65·6 per cent) had associated liver cirrhosis. Lobular resections were performed in 20 patients (three extended right lobectomies, 12 right lobectomies, and five left lobectomies), segmentectomies in 36, subsegmentectomies in 42, and partial resections in 65.

An ultrasonic dissector has been available for our use since April 1985. Data on patients were obtained from two groups: those operated on from September 1981 to March 1985 ($n = 58$) and those operated on from April 1985 to December 1988 ($n = 105$). We compared the clinical and laboratory data, perioperative management, and the postoperative course of the two groups. Specific perioperative treatment such as intrasplenic administration of OK-432, postoperative mechanical ventilation for 18–93 h and plasma exchange therapy for persisting jaundice were carried out for 16 and zero, zero and seven, and nine and one patients in the earlier and the recent periods, respectively. Serious complications were classified as intra-abdominal bleeding, bile leakage, intra-abdominal abscess, a total serum bilirubin exceeding 85 μmol/l and persisting for more than 7 days, upper gastrointestinal bleeding, and uncontrollable ascites. Death within 30 days of operation was defined as operative death, and that during hospitalization was defined as hospital death.

Hospital costs were computed for each patient (by the administrative services of our hospital) to include the following: room and board, costs of laboratory, radiology, blood and blood products, operating room/recovery room costs, and central supply/drug costs, exclusive of physician fees. Statistical analyses were made using the χ^2 and Student's t tests, and P values less than 0·05 were considered significant. Values were expressed as mean(s.d.).

Results

Clinical and laboratory data

The number of liver resections for hepatocellular carcinoma per year is shown in *Figure 1*. There were numerous increases in the number of relatively small cancers in 1987–88. Patient data are shown in *Table 1*. There were no significant differences between the two groups with respect to the clinical data other than serum α-fetoprotein levels.

Laboratory data on admission are shown in *Table 2*. During the recent period, the values of total serum bilirubin, indocyanine green test results and prothrombin time were significantly better than those in patients seen in the earlier period.

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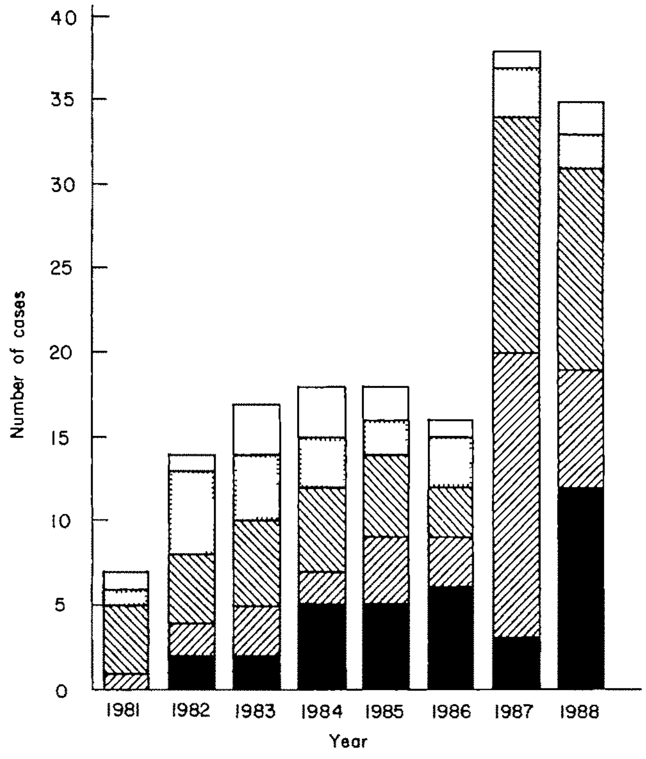

Figure 1 *Number of liver resections per year for hepatocellular carcinoma and distribution of the tumours according to the maximal diameter of the resected specimen.* ■, *≤2 cm,* ■, *>2 cm to ≤3 cm;* ■, *>3 cm to ≤5 cm;* □, *>5 cm to ≤10 cm, and* □, *>10 cm*

Table 1 *Clinical data on 163 patients with hepatocellular carcinoma*

	Period of study		
	1981–85 (*n*=58)	1985–88 (*n*=105)	*P*
Age (years, mean(s.d.))	54 7(7 4)	57 2(9·3)	n s.
Sex (men:women)	47:11	89:16	n s
Height (cm; mean(s d.))	161 7(6·3)	160 4(7 8)	n.s.
Weight (kg; mean(s.d))	56 4(8·1)	56 5(8 4)	n s.
HBsAg positive	18 (31)	20 (19 0)	n s
α-Fetoprotein >20 ng/ml	43 (74)	52 (49·5)	<0 01
Cirrhosis	42 (72)	65 (61·9)	n.s
History of			
Alcohol ingestion	33 (57)	57 (54 3)	n s.
Blood transfusion	6 (10)	21 (20 0)	n.s
Smoking	31 (53)	63 (60 0)	n.s.
Upper abdominal exploration	12 (21)	25 (23·8)	n.s.
Associated condition			
Oesophageal varices	24 (41)	32 (30 5)	n.s.
Peptic ulcer	10 (17)	12 (11·4)	n s
Cholelithiasis	7 (12)	8 (7·6)	n.s.
Ischaemic heart disease	2 (3)	4 (3 8)	n.s.
Obstructive lung disease	5 (9)	6 (5·7)	n s

Values in parentheses are percentages unless otherwise stated; HBsAg, hepatitis B surface antigen; n s., not significant

Operations

Preliminary hilar dissection for control of the vascular structures was performed in four of 58 patients (7 per cent) and 70 of 105 patients (66 7 per cent) ($P<0·01$), respectively. Intraoperative ultrasonography was performed in all patients. During the recent period, an ultrasonic dissector was used for division of the liver in about three-quarters of the patients (*Table 3*). During the recent period, mean operation time and mean anaesthesia time were significantly longer than in the earlier period (*Table 4*). However, mean estimated blood loss and mean intraoperative blood replacement were significantly lower than in the earlier period. Hepatic resection was carried out in four of 58 and 53 of 105 patients without intraoperative blood replacement ($P<0·01$). Mean intraoperative parenteral water replacement in the recent period was significantly greater than that in the earlier period but perioperative plasma replacement was less. The mean intraoperative urine output was 768 ml and 685 ml respectively, with no statistical difference between the groups. The weight of the resected liver in the recent period was significantly less than that in the earlier period (*Table 4*).

Table 2 *Laboratory data on admission*

	Period of study		
	1981–85 (*n*=58)	1985–88 (*n*=105)	*P*
Serum albumin (35–50 g/l)*	36·8(4·2)	37 0(4·3)	n.s.
Total bilirubin (4–20 μmol/l)	16·3(8 2)	13·3(5·4)	<0 01
SGOT (0–40 units/l)	99·6(76·3)	83·0(50·7)	n s.
SGPT (0–40 units/l)	114·3(89·8)	108·5(80·2)	n.s
Indocyanine green test (0–10%)	21·5(10·6)	17 0(10·1)	<0·01
Prothrombin time (80–100%)	77 6(19·3)	83 8(16 4)	<0 05
Haemoglobin (12–18 g/dl)	13·1(1·6)	13·1(1·7)	n.s
Haematocrit (35–52%)	38·9(4 8)	39 3(5 1)	n.s.
Platelet count (14–44 × 10/mm)	13·1(6·8)	13 1(6·4)	n.s

Values are mean(s d); * normal ranges are given in parentheses; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase, n.s., not significant

Table 3 *Difference in operative methods*

	Period of study		
Operative method	1981–85 (*n*=58)	1985–88 (*n*=105)	*P*
Hepatic hilar dissection			
Yes	4 (7)	70 (66·7)	<0 01
No	54 (93)	35 (33·3)	
Intraoperative aids			
Ultrasonography	58 (100)	105 (100)	n s
Liver clamps	36 (62)	4 (3 8)	<0·01
Ultrasonic dissector	0	78 (74 3)	<0 01
Microwave tissue coagulator	0	57 (54·3)	<0 01

Values in parentheses are percentages; n.s , not significant

Table 4 *Intraoperative risk factors and management*

	Period of study		
	1981–85 (*n*=58)	1985–88 (*n*=105)	*P*
Operation time (min)	174(61)	313(89)	<0 001
Anaesthesia time (min)	304(84)	446(107)	<0·001
Intraoperative blood loss (ml)	2510(2155)	1317(920)	<0 001
Intraoperative red blood cell transfusion			
Yes	54	52	<0 01
No	4	53	
Volume/patient (ml)	2200(1900)	560(830)	<0·001
Intraoperative water replacement (ml)	2730(1000)	3380(1130)	<0 001
Intraoperative urine output (ml)	768(533)	685(389)	n s
Plasma replacement during operation and up to seventh postoperative day (ml)	3771(2138)	1098(1541)	<0·001
Weight of resected liver (g)	334(350)	214(253)	<0·02

Values are mean(s.d.); n.s , not significant

Table 5 *Morbidity and mortality rates*

	Period of study		
	1981–85 ($n=58$)	1985–88 ($n=105$)	P
Complications			
No	28 (48)	80 (76·2)	<0·01
Yes	30 (52)	25 (23·8)	
Intra-abdominal bleeding	6 (10)	3 (2·9)	n.s.
Bile leakage	1 (2)	6 (5·7)	n.s.
Intra-abdominal abscess	7 (12)	8 (7·6)	n.s
Persistent hyperbilirubinaemia	17 (29)	1 (1·0)	<0·01
Upper gastrointestinal bleeding	7 (12)	2 (1·9)	<0·05
Uncontrollable ascites	11 (19)	12 (11·4)	n.s.
Operative deaths	5 (9)	0	<0·01
Hospital deaths	17 (29)	2 (1·9)	<0·01

Values in parentheses are percentages, n.s., not significant

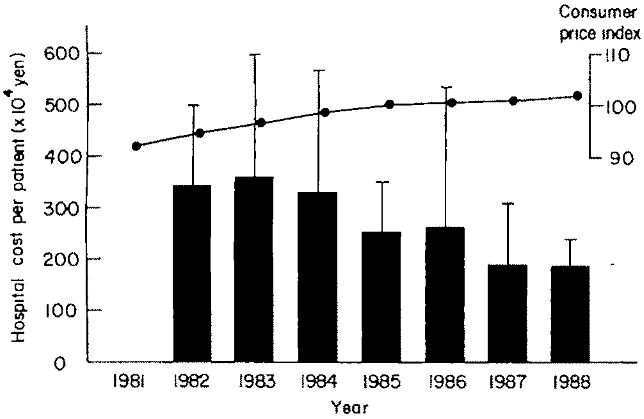

Figure 2 *Serial changes of hospital cost per patient by hospital service and the consumer price index of Japan*

A major postoperative complication developed in 30 of 58 (52 per cent) and 25 of 105 patients (23·8 per cent) respectively ($P<0{\cdot}01$). There were significant differences in the incidence of persistent hyperbilirubinaemia and upper gastrointestinal bleeding Operative death rates (9 per cent *versus* zero, $P<0{\cdot}01$) and hospital death rates (29 *versus* 1·9 per cent, $P<0{\cdot}01$) were significantly reduced in the recent period (*Table 5*).

Hospital cost

Figure 2 shows the financial cost of treating a patient. The mean(s.d.) cost was significantly reduced from 3 490 000 (2 270 000) yen (approximately 15 200(9900) pounds sterling) in the earlier period to 2 050 000(1 350 000) yen (approximately 8900(5900) pounds sterling) in the recent period ($P<0{\cdot}001$). It has decreased from 3 460 000 yen (15 000 pounds sterling) in 1982 to 1 870 000 yen (8100 pounds sterling) in 1988, despite a rise in the consumer price index of Japan from 92·2 points in 1981 to 101·7 points in 1988.

Discussion

Possible causes for the marked decline in operative morbidity and mortality rates from liver surgery are: (1) an increase in the number of relatively small hepatocellular carcinomas; (2) strict patient selection; and (3) introduction of a new therapeutic armamentarium. Gastroenterology units in Japan have a screening programme in which patients with established or suspected cirrhosis and chronic hepatitis are followed regularly by ultrasonic examination combined with α-fetoprotein measurements. The value of ultrasound in the diagnosis of hepatocellular cancer was confirmed by the fact that the identification of α-fetoprotein-negative and relatively small hepatocellular cancers has increased in recent years. To treat a patient with small hepatocellular cancer plus cirrhosis, segmentectomy instead of a typical lobectomy can be undertaken and an excessive amount of liver tissue need not be excized.

The incidence of accompanying liver cirrhosis was not statistically significant in the two periods assessed although the indocyanine green test results and prothrombin times reflect careful selection of patients for surgery. The introduction of conservative treatments such as regional chemotherapy[13] has also played an important role in this careful selection of patients for surgery.

Most liver transections in the earlier period were performed using liver clamps[14] after mobilization of the liver, and vascular control at the hepatic hilus was given less attention. In the recent period, we have used an ultrasonic dissector[15] for transection combined with preresectional vascular control of vessels supplying the hemiliver containing the lesion[16] or sometimes Pringle's manoeuvre[17] Ekberg *et al.*[18] reported no significant difference with respect to intraoperative blood loss between the primary parenchymal approach with intrahepatic ligation of all vessels and the technique of preliminary vascular control. When an ultrasonic dissector is used, a vascular clamp at the hepatic hilus need not be used to control bleeding throughout the transection; however, it is an extremely useful technique for vascular control, at least in the event of unexpected bleeding during the transection. We have routinely used intraoperative ultrasound since September 1981 to locate small tumours or daughter nodules, and agree with Rifkin and colleagues[19] regarding the value of intraoperative ultrasonography.

We have done a limited hepatic resection for relatively small hepatocellular cancers[20,21] because extensive hepatic resection may be unduly hazardous and life-threatening in cirrhotic patients and, in addition, recurrences were found to be rare at the resected hepatic stump[9].

While the use of new tools has prolonged the operation time, intraoperative blood loss combined with blood replacement was reduced and intraoperative management was simplified. Half of the patients treated in the recent period required no blood transfusion and only a small amount of plasma replacement was needed around the time of operation. Our current policy is that fresh frozen plasma should not be used in liver surgery given the risk of transfusion-transmitted disease[22].

The reduction in the incidence of hyperbilirubinaemia in the recent period may be due to the smaller number of red blood cells transfused or to the fact that less liver has been excised. The reduction in the cost per patient in the recent period is also evidence of simplified perioperative management

In our clinical experience, the new technology, despite the fact that it increases the operating time, does reduce the overall cost, morbidity and mortality rates in patients undergoing hepatic resection.

Acknowledgements

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Short note

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Emergency arterial reconstruction for acute ischaemia

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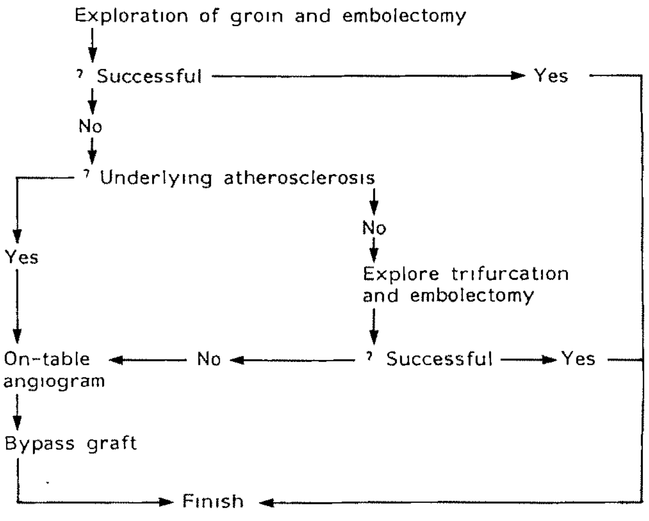
Surgical treatment of the acutely ischaemic limb was revolutionized in 1963 with the introduction of the Fogarty balloon embolectomy catheter[1]. Since then, however, the presentation of arterial thromboembolism has changed. The decline in rheumatic heart disease has been offset by a rise in ischaemic heart disease, which is frequently associated with peripheral vascular disease. Emboli, therefore, are increasingly likely to pass into a diseased vascular tree[2] and acute thromboses may form in atherosclerotic arteries. This has led to a fall in the success rate of embolectomy[3]. This unit has employed a policy of emergency arterial reconstruction when embolectomy has not achieved successful revascularization of the acutely ischaemic limb. The results are presented below.

Patients and methods

The series comprises all patients with acute lower limb ischaemia presenting to one consultant from 1985 to 1989. All limbs met criteria for defining acute limb-threatening ischaemia in that each had suffered an acute episode rendering it numb, paralysed, with no distal pulses or Doppler signals and fresh intra-arterial thrombus or embolus found at operation.

There were 62 patients (with 73 acutely ischaemic limbs) of whom 43 (69 per cent) were men and 8 (13 per cent) were diabetic Forty-five per cent had electrocardiographic evidence of recent myocardial infarction and 41 per cent were in atrial fibrillation. The median age was 69 years (range 39–88 years). The median delay from onset of the acute episode to presentation was 5·5 h (range 2 h to 17 days)

Urgent embolectomy was always attempted for potentially recoverable limbs, even if the patient presented several days after the acute event. Preoperative angiography was not performed. Peroperative management is summarized in *Figure 1* A femoral approach was employed unless the presence of a popliteal pulse prompted a primary popliteal exploration After successful embolectomy an intravenous infusion of heparin was commenced and warfarin was introduced after 3 days. If embolectomy was unsuccessful (distal pulses did not return) the degree of atheroma in the vessels was determined by their appearance and the feel of the Fogarty catheter on passage and withdrawal. If it was felt that embolectomy had been incomplete (i.e. poor backbleeding from good vessels) the popliteal artery was explored and a trifurcation embolectomy performed If this failed to restore foot



Exploration of groin and embolectomy
? Successful
Yes
No
? Underlying atherosclerosis
No
Yes
Explore trifurcation and embolectomy
On-table angiogram
No
? Successful
Yes
Bypass graft
Finish

Figure 1 *Treatment of acutely ischaemic limb algorithm*

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Table 1 *Arterial reconstruction for acute ischaemia*

Procedure	Patients	Limbs at risk	Deaths	Amputations	Fasciotomies	Limb salvage
Inflow	9	15	2	1	3	10
Patch angioplasty	12	12	2	2	2	8
Femorodistal	15	15	3	4	3	8
Total	36	42	7	7	8	26

pulses, or if the vessels were obviously diseased at the time of groin exploration, an on-table angiogram was performed and reconstructive surgery planned. Inflow procedures for proximal stenoses were performed without angiography if the downbleed was poor. Fasciotomy was performed selectively: at the time of surgery if there was obvious muscle necrosis or a considerable delay in presentation, or subsequently if signs of compartment syndrome developed. Local or regional anaesthesia was employed preferentially in the presence of known cardiopulmonary disease.

Results

Four patients with bilateral ischaemia were moribund on admission and were treated by symptom relief alone. In four patients the limb was gangrenous, requiring primary amputation (bilateral in one patient). Embolectomy was successful in 18 patients, in 13 by a femoral approach, in two by a popliteal approach and in three cases by a combined femoral and popliteal procedure. Six of these patients died. All limbs were successfully salvaged in survivors. Therefore 12 of 18 limbs were saved by embolectomy.

In 36 patients with 42 limbs at risk embolectomy failed to salvage the limb and so they proceeded to arterial reconstruction. The results of surgery are summarized in *Table 1*. The inflow procedures were three aortobifemoral, three axillobifemoral and three cross-femoral grafts. Patch angioplasty was carried out for short stenoses at arterial bifurcations. One profundoplasty was performed, five femoral bifurcation patches, four popliteal trifurcation patches and two patients required both femoral and popliteal angioplasties. Patients who merely had their arteriotomy closed with a vein patch are not included in this group. All femorodistal bypasses were performed with *in situ* long saphenous vein, mainly to distal anterior tibial or peroneal arteries. Overall, 26 (62 per cent) of the 42 limbs were salvaged. The 30-day mortality rate for reconstruction was 19 per cent (seven patients).

Twenty-two patients survived reconstructive surgery with intact limbs They have been followed up for a median period of 19 months (range 2–47 months). Two patients have died, one of breast cancer (19 months) and one from myocardial infarction (36 months). Both had functioning grafts at their last outpatient visit. The remaining 20 patients are all mobile, with functioning grafts and viable limbs. None has required further surgery. The long-term graft survival is therefore 100 per cent so far, with continued limb salvage in 91 per cent (9 per cent mortality).

Discussion

Treatment of the acutely ischaemic limb remains a challenge to the vascular surgeon. The success of balloon embolectomy will be limited as the incidence of peripheral vascular disease increases[4]. In an attempt to improve results and lower the mortality rate of the condition, thrombolytic therapy using low dose intra-arterial streptokinase has been advocated[5] but this technique is not suitable for limb-threatening acute ischaemia as defined in this series[6].

Patients should not be denied limb-saving surgery on the basis of a delayed presentation or poor 'runoff' seen on a preoperative angiogram. It is possible to perform successful embolectomy several days or even weeks after the acute episode[7] Our experience in treating chronic ischaemia has led us to question the use of preoperative angiography[8]. It will tend to underestimate the potential 'runoff' and this is especially true in the acute situation with fresh clot in the peripheral vascular tree. On-table angiography after embolectomy is better at detecting patent peripheral vessels[9].

Differentiation has not been made between embolism and thrombosis because it is often impossible to distinguish between the two, even after surgical exploration[10]. Moreover, initial treatment would be identical, with exploration of the groin and on-table angiography.

The mortality rate in this series was 19 per cent for reconstructive surgery and 33 per cent for embolectomy Thirteen patients died, only two of them having received a general anaesthetic Ischaemic heart disease was the cause of death in nine cases. Most deaths, therefore, were attributable to the poor medical condition of the patient and not to complications of surgery. All survivors were successfully returned to the community.

Thrombolytic therapy will benefit a selected group of patients when the viability of an acutely ischaemic limb is not immediately threatened. Emergency arterial reconstruction is the treatment of choice when embolectomy has failed to salvage the limb and urgent reperfusion is necessary for the limb to be saved. We believe that our policy of emergency arterial reconstruction for acute ischaemia is worthwhile, with a 79 per cent limb salvage rate in survivors and excellent long-term patency rates.

In this series, reconstructive surgery was required in 36 of 54 patients undergoing embolectomy for acute limb-threatening ischaemia. Patients with an acutely ischaemic limb are likely to have underlying peripheral vascular disease, requiring a more extensive procedure than simple balloon embolectomy to achieve limb salvage. We recommend that patients presenting with acute ischaemia should be assessed and treated by experienced vascular surgeons and that embolectomy should not be delegated to the junior surgical trainee.

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Case report

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Arteriovenous fistula in the presence of subclavian vein thrombosis: a serious complication

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The proximal veins of the upper extremity are being used increasingly for temporary access for haemodialysis[1,2]. Thrombosis is a known complication of catheterization of the subclavian vein[3–5] and its incidence is probably greater than is commonly appreciated, since it usually produces few if any symptoms[6,7]. However, subclavian vein thrombosis in the presence of an arteriovenous fistula may produce severe symptoms. This is a report of two patients who developed massive oedema of the upper extremity following the construction of an arteriovenous fistula.

Case 1

A 25-year-old man presented with loin pain, haematuria and proteinuria following an attack of tonsillitis. Renal biopsy showed severe glomerulonephritis. Six months later the patient presented in end-stage renal failure and was commenced on dialysis via a catheter placed in the right subclavian vein. A brachial arteriovenous fistula was fashioned in the left arm but this failed. A fistula was then fashioned in the right arm. Two weeks later the patient presented with a painful, swollen right arm and a venogram demonstrated thrombosis of the right subclavian vein. Since the fistula could not be used for dialysis, a Tenckhoff catheter was inserted into the peritoneal cavity and peritoneal dialysis was commenced. The arm was initially treated conservatively with anticoagulation, elevation, physiotherapy and analgesia Pain and swelling increased, however, and there was a significant functional deficit. Since the patient had become totally incapacitated it was initially decided to sacrifice the fistula by surgical ligation, but a blistering skin reaction with many large blebs developed on the arm and precluded operation. The fistula was, therefore, occluded by direct puncture and insertion of a Gianturco® (Cook Incorporated, Bloomington, Illinois, USA) coil. The pain and swelling improved almost immediately, the blebs disappeared, and the use of the arm returned to normal.

Case 2

A 41-year-old man presented with end-stage renal failure from rapidly progressive glomerulonephritis. He was initially treated with haemodialysis via an indwelling central venous catheter placed in the right subclavian vein Permanent vascular access for long-term haemodialysis was created in the form of a brachial–cephalic arteriovenous fistula in the right arm Haemodialysis was continued via the subclavian vein catheter while the arteriovenous fistula matured. Soon after the establishment of the fistula the patient complained of swelling of the right arm. This rapidly progressed to a massively swollen and extremely painful arm with significant functional disability A diagnosis of subclavian vein thrombosis was made, and the patient was initially treated conservatively with elevation of the arm, heparinization and physiotherapy. However, he remained severely disabled because of the extensive swelling and extreme pain The fistula was punctured and occluded by inserting a Gianturco coil. A Tenckhoff catheter was placed into the peritoneal cavity and peritoneal dialysis was commenced. Following successful occlusion of the arteriovenous fistula, the swelling, pain and functional deficit in the right arm rapidly resolved.

Discussion

Thrombosis of the subclavian vein is an uncommon complication related to the placement of catheters for hyperalimentation, antibiotic administration and haemodialysis[3–5,8]. On its own, the thrombosis produces hardly any symptoms, but in the presence of an ipsilateral arteriovenous fistula, resulting in increased blood flow to the arm, it can result in severe pain and gross, debilitating oedema[6,7].

Patients with a massive oedema of the upper extremity in the presence of an arteriovenous fistula do not present a diagnostic problem. However, an attempt at precise localization and determination of the proximal extent of the thrombosis may be necessary, especially if some form of diversion is contemplated. Non-invasive tests are not easy to perform and phlebography is often precluded by the venous hypertension and massive oedema[9,10].

Conservative treatment of subclavian vein thrombosis in the presence of an arteriovenous fistula, including elevation and anticoagulation, is invariably unsuccessful[7]. While the arteriovenous fistula may be salvaged by bypassing the occluded part of the subclavian vein[7], this obviously involves major vascular surgery. Otherwise, however, the fistula must be sacrificed[6]. Surgical ligation is the most obvious method but this may be difficult if there is severe and long-standing oedema. Percutaneous embolization is an attractive and less invasive alternative treatment. In both of the present cases the arteriovenous fistula was occluded by radiologists using a Gianturco coil, which allowed rapid and complete resolution of symptoms.

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Case report

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Painful lymphatic occlusion following axillary lymph node surgery

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We report a complication of axillary node surgery for breast carcinoma. The condition presents within 4–6 weeks of operation as extreme pain on abduction of the shoulder, and in one case on extension of the elbow, associated with taut wire like subcutaneous bands stretching across the axilla and occasionally to the elbow.

Case reports

Case 1

A 51-year-old woman underwent left radical mastectomy in 1978 for florid cribriform epitheliosis, not amounting to carcinoma. The specimen contained six axillary lymph nodes but no carcinoma. A month later she presented with inability to abduct the arm due to tender taut bands across the apex of the axilla. She died from asthma in 1984.

Case 2

A 58-year-old woman had a local excision and left axillary node biopsy for a moderately differentiated infiltrating duct carcinoma of the breast in 1984. Four weeks later she complained of painful bands in the axilla preventing her raising her arm

Case 3

A 73-year-old woman had a moderately differentiated infiltrating duct carcinoma of the right breast on excision biopsy. She was treated by simple mastectomy and axillary node clearance in 1984 Six axillary nodes were free of tumour. A month later she developed inability to abduct the arm owing to painful bands in the axilla.

Case 4

A 44-year-old woman underwent right simple mastectomy and axillary lymph node clearance with synchronous insertion of a subpectoral silastic implant in 1984 for a moderately differentiated infiltrating duct carcinoma of the breast with 13 out of 14 nodes involved Within 6 weeks she was noted to have bands across the axilla She died from metastatic disease without local recurrence 51 months later

Case 5

A 46-year-old woman underwent left simple mastectomy and axillary lymph node clearance with synchronous insertion of a subcutaneous Silastic (Dow Corning, Reading, UK) implant in September 1988 for a moderately differentiated infiltrating duct carcinoma of the breast involving two out of 12 axillary nodes examined She presented 1 month later with tense bands in the axilla extending visibly down the arm to the front of the elbow. On stretching, these were acutely painful and limited movement.

Management

All patients were given postoperative physiotherapy to maintain arm movements. None received any adjuvant therapy before the syndrome appeared and none exhibited lymphoedema of the arm at any time. Cases 2, 3 and 5 are currently well.

Under a general anaesthetic the arm was abducted on a board. The bands remained taut and unyielding. Open division and biopsy was performed, though in case 5 there were so many bands that finger pressure was applied and proved partially successful. The bands were easily defined and accentuated by tension. Physiotherapy was used to treat the residual bands in case 5 over a period of a few weeks.

Histology

Tissue from the taut bands was excised and examined histologically in all the cases except case 4. In cases 3 and 5, this tissue was seen to be an occluded vessel, the appearances of which were consistent with a thrombosed lymphatic vessel. In case 1, the tissue excised was a nerve trunk in which the perineural lymphatics were dilated, some containing inspissated material. In no case was there histological evidence of lymphangitis or permeation of lymphatic vessels by carcinoma. In case 2, histology showed only collagenous tissue with a few capillaries.

Discussion

The clinical presentation is unmistakable with intense pain on stretching of the taut bands which are easily visible and very tender on palpation. Klingelhofer and Conrad[1] report four cases of intercostobrachial nerve pain after axillary surgery but this would seem to be a separate entity. The natural history seems to be resolution over several weeks but surgery allows rapid relief. Subcutaneous blind division under local anaesthetic might be possible if abduction will allow access but this does not allow easy biopsy

It seems that the underlying pathological process is lymphatic thrombosis. Lymph stasis occurs after axillary lymph node surgery because of disruption of the normal lymphatic drainage channels. Tissue necrosis and infection have both been shown to hasten coagulation of lymph in conjunction with lymphatic obstruction[2]. Lymphoedema occurs following the surgical treatment of breast cancer in up to 14 per cent of patients depending on the extent of axillary surgery, radiotherapy and lymph node involvement[3]. It is attributed to lymphatic obstruction causing stasis and giving rise to exudation of a protein-rich fluid into the interstitial space, evoking a fibroblastic response

This condition is quite distinct from lymphoedema although probably a manifestation of lymph stasis. Spontaneous resolution may be due to re-establishment of the continuity of lymphatic drainage channels[2]. A cardinal feature of the condition is the severe pain and tenderness, possibly a result at least in part, of the engorgement of perineural lymphatic vessels, as seen in case 1. Why lymph stasis should lead in some patients to lymphoedema and in others to the development of taut, tender, thrombosed lymphatic vessels is unexplained.

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Original communications

Recurrence in early gastric cancer

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In a retrospective study of 503 cases of early gastric cancer, 17 of the patients had died of a recurrence of the gastric cancer and 72 had died of unrelated causes. The cumulative recurrence mortality rates were 2.2% at 9 years for mucosal cancer and 8.4% at 8 years for submucosal cancer. The recurrence patterns of early gastric cancer were hematogenic metastasis to the liver, lung, or bone (nine cases), recurrence from lymph nodes (three cases), and recurrence in the residual stomach (five cases). Submucosal cancers with a macroscopically elevated appearance, lymph node metastasis, and evidence of vessel invasion were the high-risk cancers for hematogenic recurrence, and adjuvant chemotherapy should be prescribed. Two cases of lymph node recurrence were attributed to inadequacy of lymph node dissection. Because metastasis to the group 2 lymph nodes was noted in 1.5% of cases of early gastric cancer and a macroscopic diagnosis of nodal status was inaccurate, complete dissection should be performed regardless of identification of metastasis. Five cases of recurrence in the residual stomach were attributed to overlooked lesions of multiple carcinoma and were detected at an advanced stage. Careful and regular postoperative follow-up is required to detect these recurrences at an early stage. (SURGERY 1990;107:489-95.)

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WIDE PREVALENCE OF INTEREST in early gastric cancer has contributed to a considerable rise in the number of cases in both Japan and Western countries.[1-5] The prognosis after surgery for early gastric cancer is generally favorable, and the 5-year survival rate reported in the literature from Japan exceeds 90%.[1, 6-8] Although early gastric cancer is potentially curable by surgery, there are cases of a recurrence after curative resection. We reviewed our experience with early gastric cancer during a 24-year period and evaluated the following: (1) incidence and patterns of recurrence, (2) characteristic findings in the recurrent cases related to the clinicopathologic nature or surgical procedures, and (3) possibility of further improvement in the prognosis of early gastric cancer.

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11/56/17759

PATIENTS AND METHOD

We reviewed the records of 503 consecutive cases of curative resection for early gastric cancer performed at the Institute of Gastroenterology of Hofu from 1965 to 1988. Based on the results of a postoperative follow-up study conducted in March 1989, the cumulative recurrence mortality rate was calculated by the life-table method[9] in which deaths as a result of unrelated and unknown causes were managed as short follow-up cases. The χ^2 test was used for statistical analysis.

Clinicopathologic descriptions, including macroscopic classification of gastric cancer, were based on *The General Rules for the Gastric Cancer Study in Surgery and Pathology* in Japan.[10] All histologic specimens were reviewed by a senior experienced pathologist to determine the depth of gastric wall invasion, histologic type, and extent of lymphatic and vascular vessel invasion of carcinoma. In relation to lymph node dissection, the nomenclature described above[10] was used (Fig. 1; Table I). The recurrence patterns were determined by reviewing the medical records, including laboratory data ultra-

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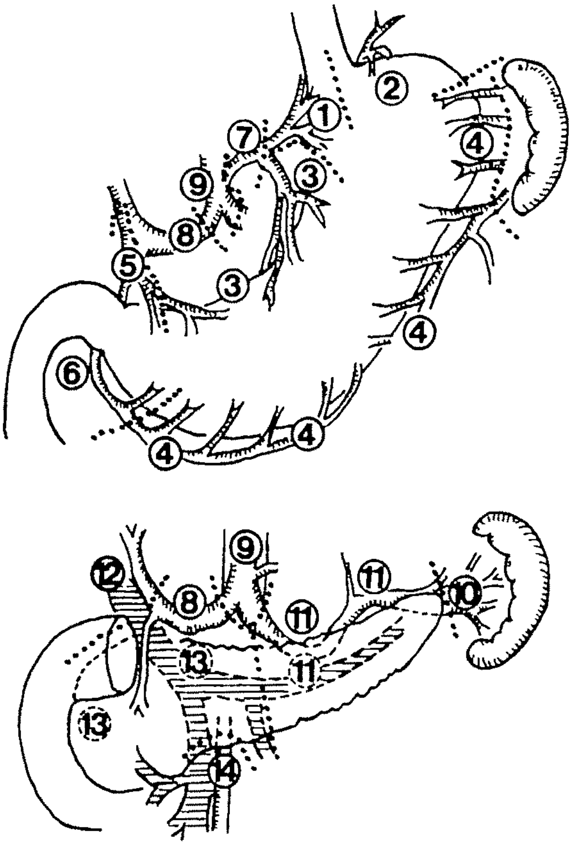

Fig. 1. Designating number of regional lymph nodes.[10] Perigastric lymph nodes: *1,* right cardial, *2,* left cardial, *3,* lesser curvature, *4,* greater curvature, *5,* suprapyloric, *6,* infrapyloric. Extraperigastric lymph nodes: *7,* left gastric artery, *8,* common hepatic artery, *9,* celiac artery, *10,* splenic hilus, *11,* splenic artery, *12,* hepatoduodenal ligament, *13,* retropancreatic; *14,* mesenteric root.

sonography, computed tomography, scintigrams, peritoneal punctures, and laparotomy

RESULTS

Incidence of recurrence. The cause of death was investigated in 97 patients. Seventy-two (74.2%) had died of unrelated causes, 8 (8.2%) of unknown causes, and the remaining 17 (17.5%) of recurrence of the gastric cancer (Table II). The cumulative recurrence mortality rates were 2.2% at 9 years for mucosal cancer and 8.4% at 8 years for submucosal cancer, and there was no case of death of recurrence later (Fig. 2). The incidence of recurrence was significantly higher in submucosal cancer ($p < 0.05$).

Patterns of recurrence and survival. The clinical courses of 17 patients who had died of recurrence are depicted in Table III Recurrence of hematogenic metastasis (liver, lung, or bone) was the most frequent (nine cases), followed by recurrence in the residual stomach (five cases) and recurrence from the lymph nodes (three cases). The peritoneal dissemination noted in one patient (case 13) was considered to be a secondary development from the cancer in the residual stomach. Of the 12 patients with a recurrence of hematogenic or lymph node metastasis, 10 (83%) died within 5 years after operation. In contrast, all five patients with a recurrence in the residual stomach survived more than 5 years.

Table I. Grouping of regional lymph nodes according to the location of tumor

Location of tumor	*Group 1 (n_1)*	*Group 2 (n_2)*	*Group 3 (n_3)*
Distal stomach	3, 4, 5, 6	1, 7, 8, 9	2, 10, 11, 12, 13, 14
Middle stomach	1, 3, 4, 5, 6	2, 7, 8, 9, 10, 11	12, 13, 14
Proximal stomach	1, 2, 3, 4	5, 6, 7, 8, 9, 10, 11	12, 13, 14

Table II. Cause of death

	No of patients according to the period of survival (yr)			*Total*	
Cause of death	*<5*	*5-10*	*>10*	*n*	*%*
Recurrence	10	7	0	17	17.5
Unrelated causes	28	19	25	72	74.2
Unknown causes	3	3	2	8	8.2
Total	41	29	27	97	100

Recurrence of hematogenic metastasis. Submucosal invasion was noted in all nine cases that resulted in recurrence of hematogenic metastasis (Table IV). Seven patients had a macroscopically elevated (including mixed types) lesion (78%), four had lymph node metastasis (44%), eight had evidence of lymph vessel invasion (89%), and seven had vascular vessel invasion (78%) To determine which type of early gastric cancer was at a high risk for a hematogenic recurrence, we compared the incidence of hematogenic recurrence in the submucosal cancer with regard to pathologic features (Table V). The incidence of hematogenic recurrence was significantly higher in macroscopically elevated types (including mixed types) (7/55 = 12.7%) than in depressed types (2/161 = 1.2%) and in lymph node metastasis-positive cases (4/32 = 12.5%) than in negative cases (5/184 = 2.7%). When focusing on evidence of vessel invasion, hematogenic recurrence was

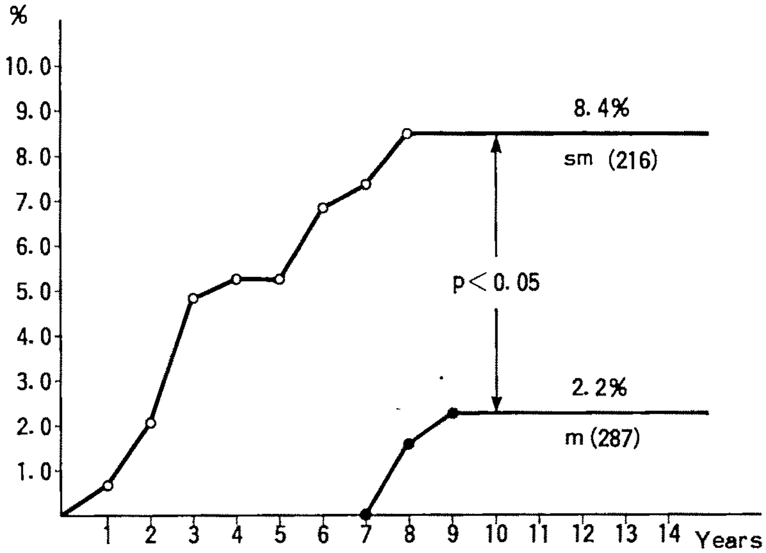

Fig. 2. Cumulative recurrence mortality rate in early gastric cancer *sm*, Submucosal cancer, *m*, mucosal cancer, *figures in parentheses*, number of of cases

Table III. Clinical course of 17 patients who died of a recurrence

Case	*Age (yr)/sex*	*Operation*	*Recurrence pattern*	*Relaparotomy**	*Survival*
1	60/M	R2	Liver metastasis	-	11 mo
2	68/F	R2	Liver metastasis	-	5 yr 11 mo
3	66/M	R2	Liver metastasis	-	2 yr 2 mo
4	68/M	R1	Liver metastasis	-	6 yr 8 mo
5	61/M	R2	Liver metastasis	-	2 yr 11 mo
6	61/M	R2	Liver metastasis	-	2 yr
7	66/M	R2	Lung metastasis	-	2 yr 10 mo
8	72/M	R2	Lung metastasis	-	3 yr 4 mo
9	81/M	R2	Bone metastasis	-	1 yr 4 mo
10	54/M	R2	Lymph node metastasis	-	1 yr 7 mo
11	70/F	R1	Lymph node metastasis	-	2 yr 4 mo
12	71/M	R1	Lymph node metastasis	-	2 yr 5 mo
13	63/M	R2	Residual Stomach	7 yr 5 mo, advanced Jejunostomy	7 yr 9 mo
14	65/M	R0	Residual stomach	-	7 yr 6 mo
15	64/M	R1	Residual stomach	6 yr 3 mo, advanced Reresection	6 yr 7 mo
16	49/M	R2	Residual stomach	5 yr 8 mo, advanced Reresection	8 yr 4 mo
17	57/M	R2	Residual stomach	4 yr 9 mo, advanced Reresection	5 yr 1 mo

R2, Gastrectomy with complete dissection of the group 2 lymph nodes, *R1*, gastrectomy with complete dissection of the group 1 lymph nodes, *R0*, gastrectomy without lymph node dissection

*Interval from the primary operation, stage of the recurrent cancer, and operation performed

much more frequent in lymph vessel invasion–positive cases (8/86 = 9.3%) than in negative cases (1/130 = 0.8%) and in vascular vessel invasion–positive cases (7/38 = 18.4%) than in negative cases (2/178 = 1.1%).

Recurrence from the lymph nodes. In three patients there was a recurrence from residual lymph nodes (Table III). In patients 11 and 12, lymph node dissection was restricted to the perigastric lymph nodes to diminish risk to the patients, because the extraperigastric nodes showed no macroscopic evidence of involvement.

Table IV. Pathologic features of the primary lesion in 17 patients who died of a recurrence

Case	*Location of tumor*	*Size (cm)*	*Gross type*	*Histologic finding*	*Depth of invasion*	*Lymph node metastasis*	*Lymph vessel invasion*	*Vascular vessel invasion*
1	A	2.0 by 2.0	IIc	Wel	sm	n_1 (+)	2	1
2	A	3.5 by 2.8	IIa	Wel	sm	n_1 (+)	2	2
3	A	3.3 by 3.2	I	Wel	sm	–	0	0
4	M	2.3 by 2.1	IIa	Mod	sm	–	2	1
5	M	4.7 by 2.0	IIa + IIc	Por	sm	–	1	1
6	C	4.1 by 3.6	IIa + IIc	Por	sm	n_1 (+)	3	1
7	A	7.0 by 3.0	I + IIa	Wel	sm	–	1	3
8	M	5.2 by 3.7	IIc + III	Por	sm	n_1 (+)	3	1
9	M	8.0 by 5.0	IIa	Wel	sm	–	1	0
10*	C	3.6 by 3.2	IIc	Mod	sm	–	2	0
	A	3.6 by 2.8	IIa	Wel	m		0	0
11	C	6.5 by 3.9	IIc + III	Por	sm	–	1	0
12	A	8.8 by 3.8	IIc	Wel	sm	n_1 (+)	1	3
13*	M	0.8 by 0.3	IIc	Mod	m	–	0	0
	A	0.4 by 0.2	IIa	Mod	m		0	0
14*	M	2.0 by 2.0	IIc	Por	m	–	0	0
	M	0.5 by 0.3	IIc	Por	m		0	0
15	M	7.0 by 4.2	I	Wel	sm	–	0	0
16	M	0.5 by 0.5	IIa	Wel	m	–	0	0
17	M	7.0 by 4.0	IIc	Mod	sm	–	0	0

A, Lower portion of the stomach, *C*, upper portion, *M*, middle portion, *Wel*, well-differentiated adenocarcinoma, *Mod*, moderately differentiated adenocarcinoma, *Por*, poorly differentiated adenocarcinoma, *sm*, invading the submucosa, *m*, limited to the mucosa, n_1 (+), metastasis in the group 1 lymph nodes, –, no metastasis, values in vessel invasion as follows 0, no invasion, 1, little invasion, 2, moderate invasion, 3, massive invasion

*Multiple lesions of carcinoma were found in the resected stomach

Two years later, massive lymph node metastasis around the celiac trunk was detected with ultrasonography and computed tomographic scanning . In patient 10, recurrence was found by the metastasis of Virchow's lymph node, although perigastric and extraperigastric nodes had been dissected adequately and proved free of metastasis (Tables III and IV).

Lymph node metastasis was histologically verified in 40 (8.4%) of 474 cases in which lymph nodes were dissected (Table VI). The rate of metastasis was 3.0% for mucosal cancer and 15.2% for submucosal cancer. Metastasis to the group 2 nodes (n_2) was noted in seven (1.5%) cases, including one case of mucosal cancer. We reviewed the anatomic distribution and intraoperative diagnosis of 61 metastatic lymph nodes in the 40 patients (Fig. 3). Forty lymph nodes (66%) were diagnosed during surgery to be free of metastasis, based on the small size or normal consistency.

Recurrence in the residual stomach. Five patients had died of a cancer in the residual stomach (Table III). Since the resected stumps had proved free of carcinoma cells, recurrence in the residual stomach is attributed to the overlooked lesions of multiple carcinoma or intragastric metastasis. In two of five cases (cases 13 and 14), multiple lesions of carcinoma were found in the resected stomach (Table IV). The stage of recurrent carcinoma was advanced and reresection was performed in three cases for purposes of palliation. All five patients died within 3 years after the diagnosis of recurrence.

DISCUSSION

The long-term postoperative follow-up study of patients with early gastric cancer revealed that a considerable number of late postoperative deaths are the result of unrelated causes and figures related to the survival rates are influenced by the average age of patients and the number of unrelated deaths[3, 5, 7] (this study). Therefore the postoperative result of early gastric cancer can be evaluated more reliably by means of the recurrence mortality rate rather than the survival rate, providing that the causes of deaths are investigated thoroughly. The cumulative recurrence mortality rate in this study was somewhat higher than the reported incidences of recurrence (2.0% to 4.0% as a whole),[1, 6, 7, 8] because the potential risk of recurrence in the cases with short follow-up was included.

There is a general agreement among investigators in Japan that the characteristic pattern of recurrence in

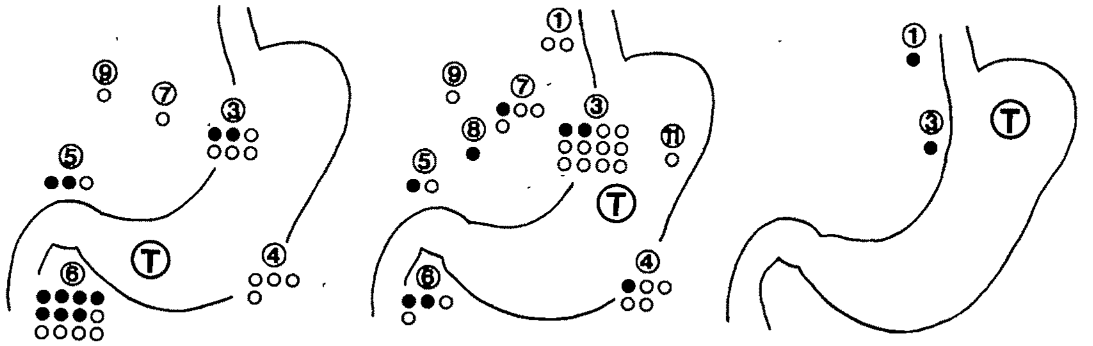

Fig. 3. Anatomic distribution and intraoperative diagnosis of 61 metastatic lymph nodes. *Closed circles,* Lymph nodes diagnosed during surgery to be involved, *open circles,* lymph nodes diagnosed during surgery to be free of metastasis, *T,* location of tumor

Table V. Comparison of the incidence of hematogenic recurrence in submucosal cancers according to various pathologic features

Pathologic features		*Incidence of hematogenic recurrence* *n*	*%*	*p Value*
Gross type	Elevated	7/55	12.7	0 01
	Depressed	2/161	1.2	
Lymph node metastasis	n (+)	4/32	12 5	0 05
	n (−)	5/184	2 7	
Lymph vessel invasion	Positive	8/86	9.3	0 01
	Negative	1/130	0.8	
Vascular vessel invasion	Positive	7/38	18 4	0.01
	Negative	2/178	1.1	
Size of tumor	<4 cm	4/130	3.1	NS
(maximum diameter)	>4 cm	5/86	5.8	
Histologic finding	Differentiated	6/126	4.8	NS
	Undifferentiated	3/90	3 3	

As to the gross types, *elevated* includes protruded type, elevated type, and mixed (combination of elevated and depressed lesion) type, *depressed* includes flat type, depressed type, and excavated type Histologically differentiated group includes well-differentiated and moderately differentiated adenocarcinomas, and undifferentiated group includes poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and others

early gastric cancer is hematogenic metastasis and it accounts for 47% to 68% of all cases of recurrence[1, 7, 8] (this study). From the United States, Lehnert et al.[5] reported four cases of recurrent cancer, three of which included a hematogenic metastasis. Nine cases of hematogenic recurrence in our study were exclusively submucosal cancers and were characterized by a macroscopically elevated appearance, lymph node metastasis, lymph vessel invasion, and vascular vessel invasion. Special subtypes of submucosal cancer such as Pen-A type and Borrmann type, characterized by macroscopically elevated appearance, were reported to have a poor prognosis because of a hematogenic recurrence.[6, 11] Those groups may be responsible for the fact that elevated types of early gastric cancer have a little lower survival rate than have depressed types.[1, 4, 8] As to vascular vessel invasion, Lehnert et al.[12] attributed the high incidence of hematogenic recurrence in early gastric cancer to the rich vascularity of the gastric mucosa. Because the primary tumor is not exposed to the serosal surface, further carcinomatous development would be attributed to vessel invasion.[13] Actually, in our study the incidence of hematogenic recurrence was significantly higher in cases of not only positive vascular vessel invasion but also lymph vessel invasion or lymph node metastasis. Thus we consider that evidence of vessel invasion is the most decisive risk factor for a hematogenic recurrence and it implies the indication of adjuvant chemotherapy

Recurrence from the lymph nodes in two patients was attributed to an inadequate lymph node dissection. Although distribution of the metastatic lymph nodes in early gastric cancer is confined mostly to the perigastric

Table VI. Nodal status in early gastric cancer

	n_0		n_1		n_2		
Depth of invasion	*n*	*%*	*n*	*%*	*n*	*%*	*Total no*
m	255	97.0	7	2.7	1	0.4	263
sm	179	84.8	26	12 3	6	2 8	211
TOTAL	434	91.6	33	7.0	7	1.5	474

n_0, No lymph node metastasis; n_1, metastasis in the group 1 lymph nodes, n_2, metastasis in the group 2 lymph nodes (see Table I), *m*, limited to the mucosa, *sm*, invading the submucosa

nodes (n_1), involvement of the extraperigastric nodes was identified in 1.5% to 3.0% of cases, including some cases of mucosal cancer[1, 2, 8, 14, 15] (this study). However, it is very difficult to identify the involved nodes during surgery (i.e., the macroscopic diagnosis of nodal status is often inaccurate).[16-18] In early gastric cancer, 66% to 79% of metastatic lymph nodes were diagnosed during surgery to be free of metastasis[15] (this study). Although Madden et al.[18] reported that the inaccuracy of intraoperative surgical staging did not cause substantial disadvantage, we found that a spontaneous regression of carcinoma in the metastatic lymph nodes left in place was unlikely to occur. Thus we consider that selective lymphadenectomy involves the risk of recurrence from residual lymph nodes. For a curative resection, perigastric and extraperigastric lymph nodes along the main arteries near the stomach should be completely dissected (R2 resection). Local resection or preservation of lymph nodes was proposed for the resection of a small mucosal carcinoma.[8, 19, 20] Reports on the nodal status in early gastric cancer revealed that lymph nodes are not involved in a polypoid mucosal cancer less than 2.0 cm in diameter,[8, 14, 20] and conservative surgery may be acceptable in such cases. However, preoperative estimation of the depth of cancerous invasion remains an open question. As Azuma et al.[21] pointed out, in patients with a preoperative diagnosis of mucosal cancer, 36% were identified histologically as having submucosal cancer. Therefore we consider that the R2 resection is essencial even in early gastric cancer, because this procedure does not affected postoperative mortality rates.[16]

Another interesting finding is our study was the high incidence of recurrence in the residual stomach (5/503 = 1.0%). The incidence of synchronous multiple gastric cancer was reported to be 6 5% to 17%.[2, 5, 6, 8, 22, 23] Mitsudomi et al.[23] reported that more than 20% of lesions of multiple gastric cancer were missed in the preoperative examination. Thus minute cancers may have existed in the residual stomach in a considerable number of patients, and such would explain the recurrence in the residual stomach. We must bear in mind the high incidence of multiple gastric cancer while engaging in the preoperative diagnosis and try to reduce the overlooking of small lesions. Recurrent carcinoma in the residual stomach is usually evident after a long postoperative period,[11] indicating that the growth of carcinoma in the residual stomach is slow. In our series, all five patients with a recurrence in the residual stomach survived for more than 5 years. Therefore if the postoperative follow-up is regular and meticulously done, any recurrent lesion in the residual stomach can be detected at an early stage and consequently reresection can be performed curatively.

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Announcement

Surgical Research Society submissions and The British Journal of Surgery

It has been observed by the editorial staff that, although the overall number of papers submitted to *The British Journal of Surgery* is increasing and we run as many pages as we have ever done, the number of papers of scientific surgical research is less. For this reason, with the approval of the President of the Surgical Research Society, Professor N. Browse, a questionnaire survey was carried out of the 100 presenters at the last Surgical Research Society meeting held in Liverpool. This brief paper presents the results of that survey.

One hundred authors were questioned. There were 71 returned responses (rather poor, especially since a stamped addressed envelope was included). Sixty-two first authors said that their work was mature and ready for publication. Nine respondents said that their work was incomplete and, of these, seven stipulated that further work was in progress in preparation for submission to a journal. One author was happy at having read a Surgical Research Society paper and to have the work abstracted in *The British Journal of Surgery*. One respondent did not specify further.

Of the 62 authors who stated that their work was ready for publication 53 per cent said they were submitting the work directly to *The British Journal of Surgery* and to no other journals. Another 8 per cent stipulated *The British Journal of Surgery* and one other named journal.

From Surgical Research Society presentations we lose six articles (10 per cent) to oncological journals, six articles to the *Lancet* and/or *New England Journal of Medicine*, five articles to the *British Medical Journal* and three to transplant or immunology journals. Two abstracts were to be presented as papers to *Gut*, one paper to *Gastroenterology*, one paper to a vascular journal, two papers to a pathology journal and one paper to *Brain Research*. Pleasingly only four respondents mentioned a desire to submit to transatlantic surgical journals. One author said he was to submit to *Lancet*, *Gastroenterology* or *Nature* and that he would only submit to *The British Journal of Surgery* if these journals did not take the manuscript!

In summary, *The British Journal of Surgery Society* and the Editorial Board were pleased to receive this data at their last meeting on 28 March. It is heartening to appreciate that over 50 per cent of papers to the Surgical Research Society will be submitted to *The British Journal of Surgery*.

The Editorial Board reiterates its desire to receive and publish as many surgical scientific papers of merit as it can handle. The Surgical Research Society will no doubt be interested to read that such a high proportion of work presented to its last meeting was mature and was not 'research in progress'.

J. R. Farndon

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Surgical Research Society Abstracts

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The following abstracts are from the papers presented at the 71st meeting of The Surgical Research Society, held at the University of Liverpool, on 11–12 January 1990.

Effects of Sandostatin in ameliorating the complications of small bowel obstruction in rats

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Mechanical bowel obstruction results in distension, strangulation, vascular compromise and necrosis of the intestine Since Sandostatin (SMS) stimulates water and electrolyte absorption and inhibits water secretion in the small bowel, we have studied its effects on intestinal secretory disturbances in rats with complete small bowel obstruction.

Six hours after construction of a 10 cm closed loop of terminal ileum, male Wistar rats were randomized to receive SMS (2 μg SC) or saline. The dosing regimen was repeated every 12 h. Twenty-four and 48 h after the start of the treatment, ileal blood flow was determined in 12 animals in each group. The rats were killed, the closed loops removed, the volume of the luminal contents measured and analysed for electrolytes, the loops weighed and a portion examined histologically

The closed loops of SMS-treated animals appeared normal macroscopically and microscopically whereas those of control animals were grossly distended with microscopic features of inflammation and necrosis. The weight of the SMS loops ($0{\cdot}891 \pm 0{\cdot}05$ g at 24 h, $1{\cdot}12 + 0{\cdot}072$ at 48 h) were significantly less ($P < 0{\cdot}001$, Student's t test) than control animals ($1{\cdot}54 \pm 0{\cdot}11$ g at 24 h; $2{\cdot}05 \pm 0{\cdot}05$ g at 48 h) but the dry weights did not differ significantly. The volume and electrolyte output of the loops in the SMS group were significantly less than in controls at 24 and 48 h Blood flow to the closed loop (in mg min^{-1} g^{-1} dry tissue) was significantly greater ($P < 0{\cdot}001$) in SMS-treated animals ($4{\cdot}6 \pm 0{\cdot}3$ at 24 h; $4{\cdot}3 \pm 0{\cdot}4$ at 48 h) than in control animals ($1{\cdot}7 \pm 0{\cdot}4$ at 24 h, $0{\cdot}9 \pm 0{\cdot}9$ at 48 h).

The results of this study suggests that SMS may be a useful adjuvant treatment to surgery in small bowel obstruction, particularly in patients with recurrent partial obstruction postoperatively

Antitropic effect of dietary calcium in subjects at increased risk for colon cancer

R.G. Wilson, W.G Brydon and A.N. Smith, *University Department of Surgery, Western General Hospital, Edinburgh EH4 2XU, UK*

Cell proliferation is increased in the large bowel of subjects at high risk of colon cancer. This abnormality has been proposed as a biomarker of cancer risk in the analysis of nutritional intervention in both human and animal models[1] It has been postulated that increased dietary calcium may be protective against colon cancer.

We have studied dietary supplementation with calcium in nine subjects with colonic polyps. Rectal biopsies before and at the end of 14 days calcium (1200 mg/day) were assessed for changes in crypt cell production rate (CCPR) and bromodeoxyuridine (BRDU) labelling. In addition, putative mechanisms for the protective effect of calcium were analysed in stool collections performed before and at the end of the study period

Mucosal proliferation decreased on oral calcium with a fall in CCPR (11 4–8 cells $\text{crypt}^{-1}\,\text{h}^{-1}$, $t = 3{\cdot}3$, $P < 0{\cdot}05$) and a significant downward shift in the distribution of BRDU labelling within the colonic crypts. Stool analysis revealed significant increases in free faecal water (median. pre 29 6%; post 45·0%; $P = 0{\cdot}03$) and calcium concentration (median. pre 178 mmol/kg; post 270 mmol/kg, $P = 0{\cdot}008$), a trend to decreased total bile acid concentration (5·1–4 0 mmol/kg, $P = 0{\cdot}08$) and a reduction in the ratio of lithocholic to deoxcholic acid (82–68, $P = 0{\cdot}007$)

Calcium reduces the abnormal proliferation in the at-risk colon. This effect is mediated by an altered faecal bile acid profile and a possible diluent effect on toxins present in the faecal stream.

1 Lipkin M. Biomarkers of increased susceptibility to gastrointestinal cancer: new application to studies of cancer prevention in human subjects *Cancer Res* 1988, **48** 235–45.

Effect of OKT3 on natural killer activity

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Natural killer (NK) cells may play a role in the immunosurveillance of malignant cells They may also be precursors of lymphokine activated killer (LAK) cells which have an antitumour effect *in vivo*, although the mode of activation is unclear The monoclonal antibody to the CD3 antigen (OKT3) has a mitogenic effect *in vitro*, leading to T-cell activation with LAK-cell proliferation. We have studied NK function *in vitro* after OKT3 pretreatment of peripheral blood lymphocytes (PBL) from normal healthy individuals. PBL, isolated by Ficoll-Hypaque centrifugation, were assessed for NK activity in a 4 h chromium-51 release assay using K562 as targets. PBL were pretreated for 30 min at 37°C with OKT3 (1·1–0·11 μg/ml) before addition of target cells. Results are expressed as lytic units, where one lytic unit (LU) is the number of effectors required for 30 per cent cytotoxicity)

	NK activity ($10^{-3} \times$ LU/10^4 PBL) in individual No.							
	1	2	3	4	5	6	7	8
Control	63	49	10	52	50	116	13	1
OKT3	163	115	57	94	79	119	54	15
Increase (%)	159	135	470	81	58	63	315	1400

OKT3 at 0.11 μg/ml: $P < 0{\cdot}001$ for each individual

OKT3 pretreatment of fresh PBL consistently enhanced NK activity in all individuals (median = 147 per cent, range 58–1400) at all OKT4 concentrations tested. These results may be due to a soluble mediator(s) produced by CD3-positive cells in enhancing the activity of CD-positive NK cells and the role of cytokine involvement is under further investigation.

Selective uptake of glutamine in the gut: confirmation in a human study

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Recent animal data suggest that the gut may play a far more important metabolic role than previously thought[1]. During critical illness disruption in bowel-barrier function may result in a chronic hypermetabolic state and contribute to multiorgan failure. Animal studies have demonstrated that the enterocytes of the gastrointestinal tract use glutamine (Gln) as a respiratory fuel and during critical illness the consumption of Gln by the gut significantly increases. The selective uptake of Gln by the gut has not, to date, been confirmed in humans Seven patients who sustained multisystem trauma necessitating laparotomy underwent portal venous catheterization This was done by reopening the umbilical vein, facilitating access to the left branch of the portal vein using a standard central venous catheter Portal venous and systemic blood samples were recorded for five days postoperatively Amino acid levels in both circulations were recorded at 48 h and 5 days. The percentage differences between individual amino acids in portal and systemic circulations were compared Student's t test for related samples was used to determine statistical significance. At 48 h, portal venous Gln was 84 ± 5 per cent (s d.) lower than systemic levels ($P < 0{\cdot}002$) At 5 days, portal Gln was 87 ± 3 per cent lower than systemic serum ($P < 0{\cdot}003$) This study confirms, for the first time in humans, that selective uptake of Gln occurs in the gut In stressed states, Gln deficiency is associated with gut mucosal atrophy This has significant implications as Gln is not provided in current parenteral nutrition formulations

1 Wilmore DW, Smith RJ, O'Dwyer ST *et al.* The gut: a central organ after surgical stress. *Surgery* 1988, **104**: 917–23

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C-erbB2 expression in primary breast cancer and its relationship to long term prognosis

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The proto-oncogene C-erbB2 codes for a protein product present at the cell surface which has considerable homology with the epithelial growth factor receptor. Initial short-term studies suggest its presence in breast cancers is associated with tumours of poor prognosis[1] and we have evaluated this in patients from a long-term prospective study.

A study was made of 391 patients with stage 1 and 2 breast cancer treated by mastectomy and receiving no adjuvant therapy between the years 1975 and 1981 The C-erbB2 protein was detected immunohistochemically and its presence or absence correlated with conventional risk factors including stage, grade and oestrogen receptor status. The data was analysed by life table methods and multiple regression analysis.

The receptor was present in 18 per cent of all tumours and was independent of all other risk factors except tumour size. The presence of C-erbB2 confers a significantly worse prognosis for both disease free period ($\chi^2=7{\cdot}813$, $P=0{\cdot}0052$) and survival ($\chi^2=7{\cdot}674$, $P=0{\cdot}0056$) Patients whose tumours failed to express the protein had a mean increase in disease free survival of 12 months

This study confirms that C-erbB2 is a significant prognostic factor but unlike other previously reported studies[1], we found it to be independent of other tumour factors which increases its usefulness in determining the long-term outlook for patients.

1. Wright C, Angus B, Nicholson S *et al.* Expression of C-erbB2 oncoprotein: indicator in human breast cancer *Cancer Res.* 1989; **49** 2087–90.

Non-invasive measurement of the physical properties of abdominal aortic aneurysms

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Rupture of abdominal aortic aneurysms occurs because of an imbalance between the physical properties of the aneurysm wall and the forces acting on it. Therefore, non-invasive assessment of these physical properties might provide a means of predicting aneurysmal rupture

We have developed a non-invasive method using simultaneous B-mode and M-mode ultrasound to measure the change in aortic diameter during the cardiac cycle. This measurement combined with measurement of blood pressure allows calculation of the pressure strain elastic modulus (PSEM), an index of the stiffness of the aortic wall (PSEM = systolic – diastolic blood pressure divided by change in aortic diameter/minimum aortic diameter, mmHg).

The PSEM of ten young (21–29 years, mean 24·6) and 10 older (65–84 years, mean 71·1) controls was compared with 10 patients with abdominal aortic aneurysm (57–78 years, mean 71·25). The PSEM of the older controls (mean PSEM = 1089, s.d. = 155) was three times that of the young controls (mean PSEM = 337, s.d. = 133, $P<0{\cdot}005$). The PSEM of patients with abdominal aortic aneurysms (mean PSEM = 3910, s.d. = 1686, was nealy four times that of the age-matched controls ($P<0{\cdot}005$). This is consistent with data obtained by invasive methods and provides a promising new method in the study of aortic aneurysms.

Characterization and significance of serotonergic receptors on enterocytes

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Serotonin (5-HT) is distributed throughout the mammalian digestive tract. The highest concentrations are in the enterochromaffin (EC) cells of the mucosal crypts. Much indirect evidence points to the existence of mucosal serotonergic receptors. However identification has proved difficult. Our hypothesis is that serotonin released from EC cells acts on receptors on the mucosal crypt cells to modify their function. Enterocytes were isolated from freshly killed guinea-pigs by a non-enzymatic vibration–chelation method. Percoll density gradient centrifugation was used to separate non-epithelial cells. Histological analysis with a monoclonal cytokeratin antibody confirmed the exclusion of other cell types. Cell viability was >95 per cent as tested by trypan blue exclusion. The physiological criteria for the existence of a receptor were met, namely that the site was saturable by increasing concentrations of [^{3}H]serotonin, binding was temperature-dependent (with maximal activity at 37°C) and antagonized by the S_2 receptor antagonist Ketanserin. Scatchard analysis revealed a K_d (dissociation constant) of $3{\cdot}3\times10^{-7}$ M and a B_{max} (maximal receptor density) of $1{\cdot}85\times10^{-7}$ M. A Hill plot approximated unity, suggesting a single population of receptors. These results confirm our hypothesis and provide an important insight into the mechanism of serotonin action in the diarrhoea of carcinoid syndrome and in the secretory disorder of the dumping syndrome.

Lymphocyte infiltration patterns in small bowel transplants

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The cellular basis of allograft rejection is complex, particularly following small bowel transplantation where the graft contains a large heterogeneous lymphoid population. The aims of this study were to monitor the pattern of graft infiltration by host cells and to evaluate the effect of cyclosporin on this process.

Heterotopic accessory vascularized small bowel transplants were performed between two highly inbred strains of rats (DA-RT1^a and PVG-RT1^c). Animals in group 1 (controls, $n=20$) received no immunosuppression, group 2 ($n=21$) received cyclosporin 15 mg kg^{-1} day^{-1} i.m. Rats were killed daily until seven days after transplantation. Graft tissues were harvested and subjected to immunohistochemical analysis using strain-specific monoclonal antibodies (MN4 vv DA class I cells, OX27 vv PVG class I cells), and an indirect immunoperoxidase technique. Control animals rejected their grafts in 7 days. cyclosporin-treated animals showed no evidence of structural damage to the graft at this time.

		Host cells (%) at day			
Graft tissue	Treatment	1	3	5	7
Lamina propria	Control	10	70	80	>80
	Cyclosporin	<5	10	10	50
Peyer's patch	Control	80	95	99	99
	Cyclosporin	<5	10	80	80

Initially there is a major invasion of graft Peyer's patches which is followed by mucosal infiltration. Successful immunosuppression with cyclosporin preserves mucosal architecture and postpones but does not prevent significant mucosal infiltration by host cells.

Assessment of the response to chemotherapy in oesophageal carcinoma

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The role of chemotherapy in the management of patients with oesophageal carcinoma is uncertain and its assessment limited by current techniques of investigation. Both CT scan and barium meal are traditionally used to measure response to treatment, but there have been no comparative studies of the accuracy of these methods, nor any attempt to correlate the results with changes in the pathological appearance of the resected specimens.

To investigate this 42 patients (35 male) mean age 62 years (range 43–74) with oesophageal carcinoma (28 adenocarcinoma, 10 squamous, 4 oat cell) were studied. All patients underwent chemotherapy (adenocarcinoma:carboplatin 8, FAM 20, squamous:MIC; oat cell:CAPOMET) followed by subtotal oesophagectomy A CT scan and barium meal were performed before and after chemotherapy and the results compared with the macroscopic and microscopic appearance of the resected specimen.

Overall 23/42 (55 per cent) patients showed a response to chemotherapy on CT compared to 17/30 (57 per cent) on barium meal and 36/41 (87 per cent) on combined pathological assessment.

A pathological response was seen in 22/23 CT-positive patients (96 per cent) compared to 14/19 CT-negative patients (74 per cent).

Macroscopic examination generally showed tumour shrinkage and healing of the ulcer base whilst microscopy showed reduction in tumour slough and re-epithelialization.

The following is concluded: CT only provides a crude index of response to chemotherapy in oesophageal carcinoma; a response on CT correlates with changes in tumour pathology; a negative response on CT does not preclude an effect on the tumour; these findings have important implications for chemotherapy in oesophageal carcinoma.

Role of duodenal juice in the development of oesophageal adenocarcinoma

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Barrett's oesophagus confers an increased risk of oesophageal adenocarcinoma The carcinogenic effect of gastro-oesophageal reflux is unknown. We investigated the effect of exposure to gastric and duodenal juice on the development of oesophageal tumours in the rat

Male Sprague Dawley rats underwent cardiaplasty to produce gastro-oesophageal reflux ($n=20$) or duodeno-oesophageal anastomosis to produce duodeno-oesophageal reflux ($n=35$) Thirty animals had no operation. A carcinogen known to produce squamous tumours in rat oesophagus (2,6-dimethylnitrosmorpholine, DMNM) was administered by intraperitoneal injection to approximately half of each operated group

After 4 months of DMNN, 13 of 20 rats with duodeno-oesophageal reflux developed oesophageal carcinoma, a rate significantly higher than those with no operation (3 of 12) or gastro-oesophageal reflux (2 of 10) ($P<0·05$, Fisher exact test) Adenocarcinoma was present only in animals with duodeno-oesophageal reflux (7 of 13) In the absence of DMNN, one of 15 with duodeno-oesophageal reflux developed adenocarcinoma

The presence of duodeno-oesophageal reflux increases the frequency and changes the histological type of oesophageal cancer in the carcinogen-treated rat This supports the hypothesis that gastro-oesophageal reflux disease, in conjunction with duodenogastric reflux, may play a role in the development of oesophageal adenocarcinoma in man

Evaluation of ethylcellulose microcapsules of mitomycin in patients with liver metastases

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At present, the potential value of intra-arterial chemotherapy is limited by systemic toxicity It is known that encapsulation of cryotoxic agents into slow release particles, which are trapped in the capillary bed following arterial administration, increases exposure in the target organ and reduces systemic drug levels in animal models[1]

The aim of this study was to measure systemic drug exposure following hepatic arterial administration of microencapsulated mitomycin (MMC) in patients with liver metastases

Two pharmacokinetic studies were performed 6 weeks apart in six patients, 20 mg microencapsulated MMC and 20 mg MMC in solution were administered as a bolus via the hepatic artery

	MMC microcapsules	MMC in solution
Clearance (l h^{-1})	140 ±31	46 ±8*
Half-life (h)	0·39±0·03	0·11±0·02*
Volume distribution (l)	246 ±23	33 ±4*
Peak drug concentration (ng ml^{-1})	80 ±75	812 423*

* $P<0·05$, Student's *t*-test

These results show that very little systemic exposure is associated with the microencapsulated form of mitomycin C Dose escalation should be feasible without increasing systemic toxicity.

1. Kerr DJ, Willmot N, Lewi H and McArdle CS The pharmacokinetics and distribution of adriamycin-loaded albumin microspheres following intra-arterial administration *Cancer* 1988; **62**. 878–82.

Effect of histamine and angiotensin on antibody uptake to colorectal liver metastases

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Uptake of systemically administered antibody–isotope conjugate into colorectal liver metastases does not provide a therapeutic tumour/normal tissue dose ratio. We have developed a xenograft model of human colorectal carcinoma to study manipulation of liver tumour vasculature

Human colon cancers (LS174T) expressing carcinoembryonic antigen (CEA) were grown in the liver in athymic rats. After a 3 week growth period when solid tumours had formed, an anti-CEA monocloncal antibody (A5B7) conjugated to iodine-131 was delivered systemically ($n=8$, iliolumbar vein cannula), regionally ($n=8$, hepatic artery cannula) or regionally with angiotensin II ($n=6$, dose$=4$ μg) or histamine ($n=8$, dose$=5$ mg/kg). During the 1 h infusion, liver surface blood flow was measured with a laser Doppler flowmeter The animal was recovered and after 48 h the liver and tumour were excised, weighed and radioactivity was counted (counts/min) to derive a tumour/liver radioactivity ratio.

Group	Ratio of tumour:liver radioactivity	*P* value compared to systemic
Systemic	1·78±0·66	–
Regional	2·23±0·77	n.s.
Angiotensin II	2·34±0·92	n.s.
Histamine	3·86±1·22	<0·02

There was a 25 per cent (s.d $=12$) fall in liver surface flow in animals receiving angiotensin but this lasted for only 4·12 min (s d.$=1·1$) Histamine but not angiotensin can increase antibody uptake. The short duration of the angiotensin effect on liver blood flow may explain its ineffectiveness

Paradoxical effects of chemotherapy on lymphokine-activated killer cells in colorectal cancer

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Chemotherapeutic drugs used in the treatment of advanced malignancy are generally assumed to be immunosuppressive and might diminish the potential benefit of their combination with immunotherapeutic agents. To test this hypothesis we examined the influence of 5-fluorouracil (5-FU) on the generation of lymphokine-activated killer (LAK) and natural killer (NK) cells Fifteen patients with advanced colorectal cancer were treated with 5-FU as a continuous intravenous infusion for 5 days NK activity, LAK cell generation, lectin-induced lymphocyte transformation and interleukin-2 (IL-2) production were measured before and on days 5, 14, and 28 after 5-FU infusion.

	Anti-tumour cytotoxicity (log lytic units ±s d)			
Time	NK activity (vs K562)	LAK activity (vs DAUDI)	LAK activity (vs COLO205)	Lectin-induced stimulation index
Pre	1·08±0·81	2·15±0·46	2·00±0·38	42·3±30·4
Day 5	0·94±0·96	2·32±0·59	2·03±0·53	54·9±39·1
Day 14	1·22±0·65	2·49±0·43	2·65±0·91*	44·9±41·6
Day 30	1·21±0·66	2·65±0·79*	2·50±0·63**	90·7±51·6**

*$P<0·05$, ** $P<0·02$, $n=15$

NK activity was not significantly changed by the infusion of 5-FU. Surprisingly however, compared with day 0, LAK generation was significantly augmented on days 14 and 30 in 10 of the 15 patients studied, as was the lymphocyte response to concanavalin A Preliminary data show that production of IL-2 by lectin-activated lymphocytes is increased following 5-FU. These data reveal that 5-FU is not immunosuppressive and they form the basis for the logical design of therapeutic protocols which combine 5-FU with IL-2 immunotherapy.

Frequency of chromosomal telomere shortening in human colorectal cancer and breast cancer

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Understanding the fundamental molecular mechanisms of carcinogenesis may provide accurate prognostic indicators and might lead to novel treatment approaches. We report the first demonstration of a high frequency of shortening of chromosomal telomeres in colorectal cancer. The terminal 10–15 kilobases of normal human telomeric DNA comprise repeat sequences which maintain the structural integrity of each chromosome. We have examined telomere length in blood/tumour DNA pairs from 52 colorectal and 50 breast carcinomas Twelve adenomas and 12 normal colonic mucosa samples were also analysed. DNA was digested with restriction endonuclease, gel fractionated, Southern blotted onto nylon membranes, radiolabelled telomere DNA probe hybridized to the DNA on the membranes and densitometric analysis of autoradiographs performed. Eighty eight per cent (45/52) of colon cancers and 12 per cent (6/50) of breast cancers demonstrated severe telomeric shortening compared to blood DNA controls. Adenomas and normal mucosa did not show such changes In colon cancer, telomeric shortening showed no correlation with tumour site, size or stage, ploidy level by flow cytometry, or gene losses from chromosomes 17p, 18q and 5q No correlation between telomere size and clinicopathological parameters was apparent in breast tumours. These data suggest structural chromosomal changes are important in colorectal carcinogenesis but not in breast carcinoma.

Relation of anticancer effect of tamoxifen to changes in serum bile acids

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Recent studies indicate that glycine-conjugated bile acids stimulate breast cancer cell growth but reduce ER levels, while unconjugated bile acids are inhibitory. Tamoxifen is administered orally and undergoes hepatic metabolism, and may alter the concentrations and/or relative proportions of serum bile acids by interfering in their enterohepatic circulation. Such changes may influence tumour activity and response to treatment. The major serum bile acids have therefore been studied in elderly women with breast cancer, both before (A) and during (B) treatment solely with tamoxifen (40 mg daily; 18±5 months; mean±s.e.m) Individual major 3α-hydroxy-bile acids were determined by high performance liquid chromatography and the results are shown below (mean±s e m., $n=10$)

	Concentration of bile acid, nM (%)						
	TCDC	TDC	GC	GCDC	GDC	C	CDC+DC
A	206±53	183±50	566±172	1112±195	921±208	383±78	1050±224
B	96±24	138±27	337±57	505±71*	605±99	388±125	1453±502
A	(4±1)	(4±1)	(10±2)	(26±3)	(20±3)	(9±2)	(27±6)
B	(3±1)	(4±1)	(12±2)	(16±1*)	(20±3)	(10±2)	(34±4)

T=tauro, G=glyco, C=cholic, CDC=chenodeoxycholic, DC=deoxycholic, *$P<0.01$ compared with before tamoxifen (Wilcoxon signed ranks test)

Tamoxifen appears to induce a change in the serum bile acid profile that might favour inhibition of cancer cell growth and possibly enhancement of ER concentration. Such an indirect effect of tamoxifen could be an important aspect of its anticancer activity.

Implication of transforming growth factor beta in the failure of tamoxifen treatment in breast cancer

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Transforming growth factor beta (TGF-β), a peptide growth factor, inhibits growth of breast epithelial cells *in vitro* The antioestrogen tamoxifen increases TGF-β levels (and hence inhibits these cells) *in vitro*.

We have examined the level of TGF-β mRNA expression using Northern blots and densitometry in breast tumour tissue from 45 untreated and 11 tamoxifen-treated patients.

In the 56 tumours, high TGF-β mRNA expression correlated with premenopausal status ($P=0.05$) but was independent of oestrogen receptor status, tumour size, node involvement or histopathology. In the tamoxifen-treated patients, six with clearly progressive disease had high levels of TGF-β mRNA but in the five patients with static disease, low levels were recorded.

These data suggest that circulating oestrogen at levels present in premenopausal women has no inhibitory influence on TGF-β gene transcription and may indeed enhance it. Failure of antioestrogen (tamoxifen) treatment is associated with high, rather than low, levels of TGF-β in the tumours contrary to *in vitro* findings In these latter patients, TGF-β may enhance tumour growth indirectly by paracrine promotion of stromal cells and angiogenesis or by inhibition of antitumour immunity Alternatively, autocrine growth inhibition of tumour cells may have failed through a variety of mechanisms.

Growth inhibition of colorectal cancer cells by monoclonal antibody 425 reacting with the epidermal growth factor receptor

N.N. Williams*, U. Rodeck†, M. Herlyn† (Introduced by D. Bouchier-Hayes*), *†The Wistar Institute of Anatomy and Biology, Philadelphia, PA, USA, and *Department of Surgery, Beaumont Hospital, Dublin, Ireland*

In recent years monoclonal antibodies (mAbs) reacting with tumour-associated antigens have attracted considerable interest as potential immunotherapeutic agents. Transforming growth factor alpha (TGF-α) acting via the epidermal growth factor receptor (EGF-R) has been suggested to function as an autocrine growth factor in the progression of colorectal cancer (CRC) to the metastatic stage. In this study, we characterized non-immunological anti-tumour effects of mAb 425, a monocloncal antibody which binds to the human epidermal growth factor receptor Four CRC cell lines obtained from the Scott White Clinic, Temple, Texas, USA (SW 1116, SW 948, SW 620, SW 707) were used in this study. Direct radioimmunoassays (^{125}I) were performed using human EGF and mAb 425 to determine the number of EGF-R present on each cell line Anchorage-independent growth assays for the detection of TGF-α-like activity in spent or conditioned media of the CRC cell lines was carried out using the NRK soft agar assay Stimulation growth assays were performed on the four cell lines by adding TGF-α to cells seeded in 24-well culture plates Similarly, growth inhibition assays were carried out by adding mAb 425 at differing concentrations and determining cell counts at days 1 and 14, after seeding using a Coulter cell counter.

Cell line	EGF molecules bound per cell	TGF-α (ng/ml) secretion	Inhibition with mAb 425 (%)
SW 948	5×10^4	0.6	42
SW 1116	2×10^4	3.2	68
SW 620	5×10^3	50	0
SW 707	2×10^3	50	0

mAb 425 was found to significantly inhibit growth of two of the four cell lines and the ability to achieve this was related to a low secretion of TGF-α and a responsiveness of these cell lines to exogenously added TGF-α (data not shown). This study demonstrates that in addition to immunological anti-tumour effects mAb 425 inhibits growth-factor-dependent proliferation. These findings suggest that mAb 425 may have a dual, possibly synergistic effect on EGF-R-expressing tumour cells in patients.

Assay of epidermal growth factor receptor by flow cytometry: a comparison with radio-ligand binding assay

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The epidermal growth factor receptor (EGFR) has been widely studied in relation to human breast cancer Recent work has shown a poor prognosis associated with its expression and identified a cut-off point of clinical relevance as 10 fmol/mg, using a radio-ligand binding assay (RLBA). This assay makes possible the satisfactory analysis of the majority of breast cancers for EGF binding. Small tumours and those not treated by surgery are, however, excluded.

Flow cytometry was used to analyse the human cancer cell lines A 431, HeLa, MCF 7, ZR75 1 and SKBR 3. Cells were incubated with the mouse monoclonal antibody EGFR 1 and with fluoresceinated goat anti-mouse IgG The number of fluorescent molecules bound per cell was extrapolated from a calibration line made from fluorescent beads. These results were compared with the RLBA for the same cell lines, using linear regression analysis, and achieved a strong correlation ($r=0{\cdot}895$, $P=0{\cdot}00008$). Eighteen breast tumour aspirates, stored at −70°C, were then analysed by flow cytometry after treatment with collagenase and passage through a 37 μm nylon mesh. These results were compared with their RLBA findings and again reached a strong correlation ($r=0{\cdot}923$, $P<0{\cdot}00001$)

Flow cytometry is a valuable tool for the analysis of EGFR in breast tumour aspirates both in the clinic and postoperatively.

1. Nicholson S, Sainsbury JRC, Needham GK, Chambers P, Farndon JR, Harris AL Quantitative assays of epidermal growth factor receptor in human breast cancer: cut-off points of clinical relevance. *Int. J Cancer* 1988, **42**: 36–41.

Urinary tissue factor activity in malignant disease

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The procoagulant activity of urine has been recognized for >50 years. Tissue factor (TF) is produced by certain tumours, and is increased in both tumour-associated macrophages and blood monocytes. However, there have been no studies of urinary TF levels in malignancy

Early morning urine samples were collected and assayed for tissue factor, using a chromogenic assay Eight groups were studied: controls, without inflammatory or neoplastic disease ($n=75$); rheumatoid arthritis ($n=8$), inflammatory bowel disease (IBD, $n=16$), colorectal cancer ($n=47$); patients undergoing colonoscopy ($n=33$); benign breast disease ($n=22$); breast cancer ($n=41$) and bladder cancer ($n=44$).

The nature of the urinary procoagulant was confirmed by inhibition with concanavalin A, phospholipase C and anti-TF Urinary TF was higher ($P<0{\cdot}001$) in patients with colorectal cancer (median 31·3 units; interquartile range 17·7–43·0), IBD (35·7; 20·0–44·7), breast cancer (20·4; 11·0–33·3) and bladder cancer (21·1); 12·3–34·8) than controls (8·1; 3·9–16·4) or patients with rheumatoid arthritis (6·8, 2·9–15·3) Ten of eleven colonoscopy patients subsequently found to have either carcinoma or IBD had levels above the control upper quartile, while only 5/22 with normal colonoscopy fell into this range ($p<0{\cdot}002$, χ^2 test)

These studies provide further evidence of the involvements of the haemostatic system in malignancy Our results also indicate that urinary TF may be used as a marker of colorectal pathology and may therefore provide useful diagnostic information in patients undergoing colonoscopy

Tumour markers and rapidly progressing advanced breast cancer

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Tumour markers may be used as an aid to diagnosis, to monitor progress after primary treatment, to detect recurrence during follow-up, and to monitor response to therapy in advanced disease where early knowledge of treatment failure can prevent unnecessary suffering from side-effects

Breast tumour markers have not been widely adopted due to lack of sensitivity and specificity but two recently proposed markers, Ca 15·3 and the Nottingham Biochemical Index (NBI) have offered an improvement.

We have investigated the value of these markers in women with advanced breast cancer receiving cytotoxics. Forty five patients had markers measured at six weekly intervals during treatment and results were compared with UICC status.

Six patients in each group had normal markers initially and were excluded. Of the assessable patients showing a clinical response, a falling marker was seen in 8/10 (Ca 15·3) and 4/9 (NBI) Patients with progressive disease had rising markers in 10/19 (Ca 15·3) and 13/22 (NBI) In these patients, Ca 15·3 provided a lead time of 6 weeks in one and 12 weeks in two The NBI gave lead times of 6 weeks in six and 12 weeks in two.

This study does not support the use of these marker systems in this clinical context.

Tumour-derived immunosuppressive activity is distinct from that of transforming growth factor beta

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The low *in-vivo* success rate of immunotherapy with interleukin-2 and lymphokine-activated killer (LAK) cells, may be due to direct tumour-mediated interference with anti-tumour immune function. A tumour-derived suppressive factor (TDSF), which potently inhibits the generation of tumouricidal LAK cells has recently been described. Malignant cells maintain their autonomous growth by the secretion of growth factors. These cells also secrete the growth inhibitory protein transforming growth factor beta (TGF-β), but continue to proliferate despite this. TGF-β is a small protein homodimer known to be immunosuppressive

To determine whether the activity of this TDSF is due to TGF-β we have performed a number of functional and physicochemical comparisons. Suppressive activity after molecular manipulation was assayed in a standard LAK generation assay system

	TGF-β	TDSF
pH stability range	<pH 2	pH 4·5–11·5
Denaturation (6 M urea)	No	Yes
Reduction (2-ME)	Yes	No
Molecular weight (gel filtration)	25 kDa	40–60 kDa
Anti-TGF-β neutralization	Yes	No
Isoelectric point (p*I*)	pH 6	pH 7·2

These data demonstrate that TDSF is a moiety distinct from TGF-β and is a novel immunosuppressive tumour cell product Since failure of current immunotherapeutic regimens may be caused by TDSF, definitive determination of the identity and peptide structure of TDSF may lead to the design of strategies aimed at overcoming the effects of this immunosuppressive molecule.

Characterization and manipulation of myofibroblasts in tissue culture

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Myofibroblasts (activated fibroblasts) are found in granulation tissue, scars, Dupuytren's disease and the stroma around tumours, e g. scirrhous breast carcinoma, and cause these tissues to contract Myofibroblasts from capsules around silicone tissue expanders (EC) and Dupuytren's nodules (DN) were grown in tissue culture and compared with dermal fibroblasts (FB). Six cell lines from each group were established.

Intracellular actin, which is either polymerized in contractile filaments or non-polymerized in the cytoplasm, was measured by gel electrophoresis and scanning densitometry Expander capsule myofibroblasts contained twice the amount of total actin compared to fibroblasts ($P<0{\cdot}05$) and a threefold greater ratio of polymerized to non-polymerized actin ($P<0{\cdot}01$); Dupuytren's myofibroblasts were an intermediate group.

	Actin (μg/10^4 cells)		
	EC	DN	FB
Total	1·46† (0·89–1·91)	0·78 (0·54–0·97)	0·67† (0·59–0·72)
Polymerized	0·59 (0·45–0·73)	0·20 (0·11–0·29)	0·14 (0·06–0·19)
Non-polymerized	0·90 (0·41–1·19)	0·57 (0·43–0·70)	0·60 (0·46–0·63)
Polymerized/ non-polymerized	0·71* (0·55–0·88)	0·37 (0·26–0·47)	0·21* (0·10–0·29)

Results are median (i.q range), * $P<0{\cdot}01$, † $P<0{\cdot}05$, Mann–Whitney *U* test

Tension over 12 h and prostaglandin (thromboxane) for 30 min both increased the ratio of polymerized to non-polymerized actin in all fibroblast cell lines ($P<0{\cdot}05$). This substantiates clinical and animal findings that increased tissue tension induces myofibroblast formation and suggests that thromboxane-like substances induce rapid activation of fibroblasts to myofibroblasts.

Beneficial effect of Verapamil in clinical acute renal failure

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In experimental animals Verapamil ameliorates postischaemic acute renal failure (ARF)[1]. This pilot study assessed the effect of verapamil administration during initiation of oliguric acute renal failure in critically ill patients.

Twenty one oliguric intensive care unit patients (urinary output <35 ml/h) who failed to respond to 0·5 litre fluid challenges were enrolled. Intravenous placebo (group A) or verapamil (0·1 mg/kg, group B) were administered blindly during resuscitation. Simplified acute physiology scores were 8·1 (2·7) in group A, and 7·6 (2·2) in group B. Adjunctive medical treatment was similar in both groups. Serum creatinine at enrolment and subsequent creatinine clearances were compared

Group	Serum creatine ±s.e.m. (μmol/l)		Creatinine clearance ±s.e.m (ml/min)		Survival (%)
	N	Day 0	Day 1	Day 2	
A (placebo)	12	114 (8)	51 (3)	50 (3)	92
B (verapamil)	9	133 (9)	74 (4)	67 (4)	66
ANOVA		n.s.	$P<0{\cdot}001$	$P<0{\cdot}003$	n.s

Severity of illness assessed by SAPS[2] and renal function assessed by serum creatinine were similar at enrolment. Verapamil-treated patients had significantly better renal function than controls on day 1 and 2 Verapamil improved function when administered during initiation of ARF in surgical patients

1. Leahy AL, Wait RB Verapamil, superoxide dismutase, and catalase in postischaemic renal failure. *Surgical Forum* 1984, **35**: 24–6
2. Le Gall JR, Loirat P, Alperovitch A *et al* A simplified acute physiology score for ICU patients. *Crit Care Med* 1984; 12 975–7.

Changes in muscle tone following parathyroidectomy

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Calcium is involved in the contraction of skeletal muscle and disorders of calcium metabolism have muscular manifestations. One symptom of primary hyperparathyroidism is muscle weakness Seven patients (two male, five female; age range 53–76 years) with primary hyperparathyroidism have had muscle tone measured using a computerized version of the Wartenberg pendulum test[1] before and after removal of a parathyroid adenoma This system can accurately measure small changes in muscle tone[1]. Muscle tone is denoted by the relaxation index (R^2) calculated by the computer[1] The normal range is 1·536±0·09, a low value indicates hypertonicity and a high value flacidity[1].

All patients had a fall in corrected serum calcium associated with surgery (mean±s.e.m preoperative = 3·02±0·09 mmol/l; postoperative = 2·31±0·04 mmol/l) All patients had a corresponding increase in the relaxation index (mean±s.e.m. preoperative = 1·43±0·069, postoperative 1·686±0·051).

It was noted that there was a definite relationship between calcium and muscle tone with strong inverse linear correlation between the corrected serum calcium and the relaxation index ($R=0{\cdot}863$, $P<0{\cdot}0001$).

The data shows that muscle weakness resulting from primary hyperparathyroidism is associated with increased tone of the muscle and can be corrected by surgery. Alterations in serum calcium may induce muscle symptoms due to changes in neuronal excitation rather than as a direct effect of calcium on the muscle

1. Brown RA, Lawson DA, Leslie GC, Part NJ Observations on the applicability of the Wartenberg pendulum test to healty, elderly subjects *J Neurol Neurosurg Psychiatr* 1988, **51**: 1171–7.

Effect of diltiazem on cyclosporin nephrotoxicity

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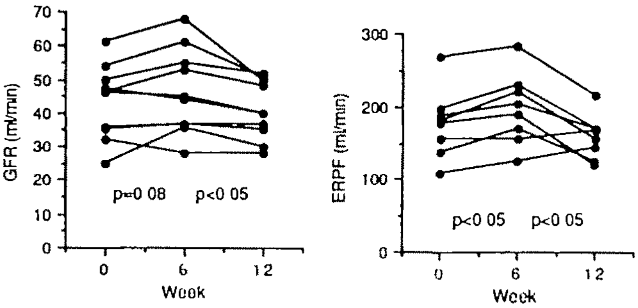
We have investigated the effect of diltiazem, a calcium channel blocking drug, on renal allograft recipients with stable renal function (creatinine <200 mmol/l for 3 months) receiving cyclosporin ($n=10$) or azathioprine and prednisolone ($n=11$). The patients were treated for 6 weeks with 60 mg diltiazem bd followed by 6 weeks without diltiazem Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by a one-shot isotope injection technique at weeks 0, 6 and 12.



P values by Wilcoxon's test

A rise and fall pattern in GFR and ERPF consequent upon diltiazem treatment was evident (binomial test, $P<0{\cdot}05$). Whole blood cyclosporin levels rose during treatment with diltiazem (Wilcoxon, $P<0{\cdot}05$) despite constant dosage. GRF was lower in the cyclosporin than the azathioprine group (Mann–Whitney *U* test, $P<0{\cdot}005$) There were no significant changes within the azathioprine group.

In stable transplant patients, diltiazem elevates whole blood cyclosporin levels but protects against the effects of cyclosporin on GFR and ERPF

Ex vivo depletion of graft T lymphocytes in small bowel transplantation

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Small bowel is unique among vascularized solid organ transplants because the large amount of organized lymphoid tissue within the graft may potentially cause graft versus host disease (GVHD). The aim of this study was to investigate whether selective *ex vivo* depletion of T lymphocytes in small bowel could prevent or delay the development of GVHD in a rat model We used OX19, an anti-CD5 T lymphocyte monoclonal antibody which was conjugated to ricin, a cytotoxic agent, to deplete T cells within the graft

Heterotopic, vascularized subtotal intestinal allografts were carried out from parent (Lewis) to F1 hybrid (Lewis × DA) inbred rats In this strain combination, GVHD develops exclusively with no concomitant rejection. In control animals (group 1) the graft was perfused with Marshall's solution In group 2 the graft was perfused with OX19 alone, and in group 3 OX19 conjugated with ricin. This conjugate and the pure OX19 were used at a dilution of 1/250, previous studies *in vitro* showed no non-specific toxicity of ricin at this concentration. All grafts were stord at 4°C for 30 min then flushed with Marshall's solution before transplantation All animals eventually developed signs of GVHD, with weight loss and diarrhoea. The survival of animals was recorded following transplantation;

Group	Treatment	*n*	Survival (mean±s.e.m.)
1	Controls	6	16·5±1·2
2	OX19	6	17·5±1·7
3	OX19+ricin	9	21·7±1·7

Using Student's *t* test, group 1 versus group 2, n.s.; group 1 versus group 3, $P<0{\cdot}05$

In this model the perfusion of small bowel allografts with an anti-T cell monoclonal antibody conjugated to ricin significantly delays the development of GVHD

A prospective study of patient choice in treatment for primary breast cancer

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The popular press (and advertisements by the ICRF) frequently implies that all women with breast cancer may be treated with breast conservation. This study was intended to evaluate the patient demand for this procedure.

One hundred and sixty-three patients with breast carcinoma were studied prospectively between January and December 1988, nine women had screen detected lesions; the remainder were symptomatic general practitioner referrals. Patients whose lesions were unifocal and measured <3 cm clinically or mammographically were offered breast conservation by excision and whole breast irradiation. Using these criteria, 56 per cent were suitable for breast conservation and were offered the choice of this or mastectomy; the others ($n=72$) were advised to have mastectomy. All patients were counselled by a trained counselling sister.

The patients' choices were as follows of patients aged ≤55, 36 chose conservation and 15 chose mastectomy, and of patients aged 56+, 15 chose conservation and 32 chose mastectomy; $\chi^2=13{\cdot}5$, (1 d.f.); $P<0{\cdot}001$.

Of 91 patients offered a choice, only 45 per cent opted for breast conservation Overall, only 27 per cent of patients were both suitable for and chose breast conservation. These results are clearly at odds with opinions expressed in the popular press.

Magnetic resonance imaging in the diagnosis of inflammatory aneurysms in the aorta

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Inflammatory aortic aneurysms comprise 10–15 per cent of all aortic aneurysms. The pre-operative diagnosis of inflammation and the involvement of other structures are important in determining surgical management Radiological diagnosis of inflammation is unreliable, and there is uncertainty regarding the best method of assessment

We retrospectively studied 279 patients with abdominal aortic aneurysms of whom 34 had inflammatory aneurysms Contrast enhanced computerized tomography (CT) correctly identified only 50 per cent of inflammatory aneurysms, a figure comparable to those published elsewhere

In a smaller, prospective series of 38 aneurysms, 9 were inflammatory. All patients underwent contrast enhanced CT and magnetic resonance imaging (MRI) of the abdominal aorta pre-operatively.

MRI correctly identified all aneurysms subsequently confirmed to be inflammatory at operation CT correctly identified only half of the inflammatory aneurysms, and gave one false positive. Of those inflammatory aneurysms identified by both methods, new, relevant information was provided by MRI only in all cases

In cases of non-inflammatory aneurysm, MRI demonstrated the origin of the renal arteries more reliably than CT. CT failed to identify the origins of the renal arteries in 25 per cent of cases

The appearances of inflammatory aortic aneurysms on MRI is characteristic and has not been described previously. Initial results suggest that MRI is superior to other methods in identifying inflammatory aortic aneurysms It is likely that MRI could be used as the sole investigation for abdominal aortic aneurysm

Tumour necrosis factor induces liver hyperplasia

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Tumor necrosis factor (TNF) mediates many of the metabolic responses following endotoxaemia, septicaemia and tissue injury. One important response to TNF is increased hepatic acute phase protein synthesis The effect of TNF on hepatic structural synthesis. The effect of TNF on hepatic structural protein and cellularity is unknown. To examine these effects, 20 parenterally fed male Wistar rats were infused with TNF (0 and 2×10^5 units $\mathrm{kg}^{-1}\ 24\ \mathrm{h}^{-1}$) for six days, wet and dry liver weight and nitrogen content were measured Liver DNA and protein, and counts of hepatocyte mitosis were determined in 48 further animals infused with TNF ($0, 2, 4\times10^5$ units $\mathrm{kg}^{-1}\ 24\ \mathrm{h}^{-1}$) over 1, 3 and 6 days.

Group	Wet liver wt(g)	Dry liver wt(g)	Liver nitrogen (g)
TNF 0	9·19±0·3	2·53±0·2	268·4±19·2*
TNF 2	13·72±0·7*	3·61±0·2*	440·3±30·2*
		Total liver DNA (mg)**	
	Day 1	Day 3	Day 6
TNF 0	27·0±1·5	25·9±1·4	19·0±0·5
TNF 2	26·6±1·3	36·8±1·9	64·6±4·1
TNF 4	25·5±1·3	43·3±2·7	49·7±4·0
		Total liver protein (g)**	
TNF 0	1·5±0·05	1·5±0·04	1·2±0·7
TNF 2	1·6±0·08	1·7±0·01	2·2±1·8
TNF 4	1·5±0·05	2·1±1·2	1·8±1·5

Results are means±s.e.m. $^{*}P<0{\cdot}0001$ versus TNF 0, $^{**}P<0{\cdot}0001$, group effect, ANOVA

TNF increased wet and dry liver weight and nitrogen content following six days of infusion. Both liver DNA and protein were increased at 3 and 6 days Histological examination demonstrated no significant inflammatory infiltrate, however, the number of hepatocyte mitoses increased with the dose of TNF and time ($P<0{\cdot}05$). These results indicate that this important inflammatory cytokine increases structural protein and induces cellular hyperplasia in the liver.

Importance of chromsome 17p in the pathogenesis of breast cancer

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The short arm of chromosome 17 (17p) has been implicated in the pathogenesis of breast cancer A gene which maps to 17p, p53, has been proposed as a tumour suppressor gene, although in mutated form p53 behaves as an oncogene.

Eighty primary breast tumours were examined for allelic loss from 17p using Southern blots of paired blood/tumour DNA p53 gene mRNA expressions in these tumours was determined from densitometry of Northern blots and the polymerase chain reaction and DNA sequencing used to identify p53 gene mutations.

Using only three polymorphic probes, YNZ22.1, MCT35.1 and BHp53, 17p allele loss was demonstrated in 42/76 (64 per cent) informative tumours. Allelic loss with probe YNZ22.1 correlated with low oestrogen receptor protein ($P=0{\cdot}029$) and overexpression of p53 mRNA ($P=0{\cdot}042$) However, p53 allele loss did not correlate with p53 mRNA overexpression. Sequencing suggested the overexpressed p53 mRNA was transcribed from mutant p53 DNA

The data confirm that 17p allele deletion occurs in a high proportion of breast cancers. Furthermore, it is proposed that deletion of a regulatory tumour suppressor locus on 17p (adjacent to YNZ) may result in overexpression of mutant, oncogenic p53 as an important step in the pathogenesis of breast cancer

Effect of ligation without stripping of the long saphenous vein

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There is still debate as to whether stripping in addition to ligation of the long saphenous vein is necessary. This study was undertaken to assess the effect of ligation alone Fifty-four limbs with long saphenous incompetence were identified by Duplex scanning The status of all other veins was also noted Photoplethysmography (PPG) was performed and refilling times recorded both with and without tourniquets A Trendelenberg operation and multiple avulsions of varicosities were performed under general anaesthetic, in all cases. Duplex scanning and PPG measurements were repeated 3 to 6 months postoperatively. The operation was also subjectively graded as 'satisfactory' or 'unsatisfactory' by the patients depending on symptoms.

Pre-operatively, PPG refilling times were normalized by tourniquets in 31 cases. Postoperatively, 14 of these had normal refilling times but 17 were still abnormal A satisfactory result was significantly more common in the group with normal refilling times ($P<0{\cdot}03$, χ^2 analysis). Duplex scanning revealed persisting reflux in the long saphenous vein in 18 of these 31 limbs There was a strong association between subjective outcome of the operation and presence or absence of reflux ($P<0{\cdot}007$, χ^2) Pre-operatively, 23 limbs had PPG refilling times that were not normalized by tourniquets None of these had improvement of refilling times postoperatively, although 11 reported a satisfactory result. Reflux was detected in 11 limbs, postoperatively. There was no association between subjective outcome and reflux ($P<0{\cdot}84$), χ^2).

By objective criteria, ligation of the long saphenous vein without stripping is not adequate to correct the haemodynamic dysfunction caused by incompetence of this vein

Presymptomatic diagnosis of familial adenomatous polyposis by DNA probe analysis

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A method of presymptomatic screening for familial adenomatous polyposis (FAP) which avoids colonic examination is highly desirable. Of at-risk individuals, 50 per cent are actually unaffected and so undergo colonic screening unnecessarily. Clinical examination may miss late onset polyps. Therefore, there is a need for an accurate, objective diagnostic test. We report the first clinical use of DNA analysis for presymptomatic diagnosis of FAP. Thirty six at-risk individuals from seven FAP families were assigned risk estimations derived from RFLP linkage analyses with five DNA probes using LINKAGE 4·7 computer programs. Diagnostic certainty ranged from 60–99·98 per cent Of 21 positive DNA diagnoses, 16 were confirmed by colonoscopy and/or ophthalmoscopy for CHRPE lesions Of the 15 negative DNA diagnoses, 13 were clinically substantiated and only 1 required follow-up. There was one false negative DNA diagnosis but diagnostic certainty was only 89 per cent in that case and so would not have altered clinical management. Since diagnostic certainty can approach 100 per cent, we propose that FAP screening protocols should include DNA analysis in suitable families

Screening for gastric cancer by gastroscopy of dyspeptic subjects identified by a dyspepsia questionnaire

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Gastric cancer is still a common cause of cancer mortality, and there has been no improvement in its prognosis this century In an endeavour to increase the rate of early diagnosis of early gastric cancer, we have instigated a population based screening programme, using a symptom questionnaire to identify dyspeptic subjects. The aim of this study was to evaluate the yield of gastric carcinoma using a postal dyspepsia questionnaire. The questionnaire was sent to 4279 subjects aged 50–75 years, of which 3790 (88·6 per cent) replied. Of those who replied, 1245 (32·9 per cent) were positive for symptoms of dyspepsia. To date we have performed gastroscopy on 599 patients from this group of dyspeptic subjects. Of 1145 subjects invited to a dyspepsia clinic the compliance was 824 (72 per cent) and 83·4 per cent of those invited for gastroscopy attended Three carcinomas were diagnosed in the questionnaire screened group, two of which were 'early gastric cancers' with disease limited to the submucosa, which were diagnosed at follow-up gastroscopy. In addition, 31 patients had a Barrett's oesophagus, 14 patients (2·3 per cent) had dysplasia, 81 (13·5 per cent) had intestinal metaplasia (IM) – a group with 'premalignant' lesions in which further malignancy may develop. These data suggest that questionnaire screening may be a viable method for the early detection of gastric carcinoma

Straight ileoanal anastomosis with myotomy: an alternative to restorative proctocolectomy?

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The introduction of the pelvic ileal reservoir by Parks and others led to better functional results after restorative proctocolectomy than those of straight ileoanal anastomosis (IAA). However, pelvic reservoirs brought problems of their own such as pouchitis, impaired emptying and added postoperative morbidity. We have assessed an alternative procedure which avoids the need for a pouch, while providing an adequate reservoir and good continence.

Thirty-six female adult beagles were randomized into the following groups to undergo total colectomy with (a) ileoanal anastomosis (IAA), controls; (b) IAA plus two 15 cm long ileal myotomies (M); (c) IAA + M plus ileal flap valve; (d) IAA plus J pouch (P). The animals were studied before operation and at 4-weekly intervals for 20 weeks.

Results	Controls	Myotomy	Valve	J pouch
Reservoir capacity (ml)	85*	138·5	119	109
Reservoir compliance (ml/mmHg)	0·64*	1·65	1·61	1·82
Mean anal pressure (mmHg)	60	51	69	57·5
Bowel frequency (No /day)	4·1*	2·0	1·9	2·3
Stool wt (g/day)	125*	68	84	75
Mortality	2/9	1/9	2/9	1/9

Results are medians. * Controls versus myotomy, $P<0{\cdot}01$; myotomy versus valve versus J pouch, n.s.

A straight ileoanal anastomisis with ileal myotomy proved to be safe and provided as large and compliant a reservoir as did the J pouch

Influence of fibroblasts on growth of human colorectal carcinoma

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Fibroblast and epithelial-mesenchymal interactions may have important influences on tumour growth and metastasis. We have investigated the effects of fibroblasts on growth of human colorectal carcinoma.

Athymic mice received a subcutaneous inguinal fat pad inoculation of 2×10^6 LS174T human colorectal carcinoma cells or 2×10^6 carcinoma cells with 2×10^6 human skin fibroblasts in 0·1 ml complete medium Animals were killed on day 20 after inoculation and the tumours excised and weighed. To assess proliferative rate, 19 animals (9 LS174T alone, 10 with fibroblasts) received an intraperitoneal injection of tritiated thymidine 20 h and bromodeoxyuridine (BrDU) 1 h prior to killing

Results (mean ± s.d)	LS174T without fibroblasts	LS174T with fibroblasts	*P* value
Animals with tumours	19/31	28/32	0·02*
Tumour weight (g)	0·92 ± 0·51	1·19 ± 1·1	n.s.
Cells labelled with BrDU	10·7 ± 0·7%	11·1 ± 1·5%	n.s.
Thymidine labelling			
Pool size (mmol/l)	0·71 ± 0·25	0·93 ± 0·22	n s
DNA extract (cpm/mg)	36·4 ± 14·0	28·1 ± 13·7	n.s.

* $\chi^2=5{\cdot}71$

The initial development but not subsequent growth of colorectal carcinomas was promoted by co-inoculation with fibroblasts. This suggests a fibroblast-mediated effect on tumour implantation

Effect of vaginal delivery on anal canal sensation

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Anal canal sensation is impaired in incontinent patients and obstetric trauma predisposes to faecal incontinence. The effect of delivery on anal sensation has been assessed by mucosal electrosensitivity in 103 primiparous women immediately after delivery and at 6 months in 46 of these women There were 30 normal deliveries, 31 forceps, 17 Ventouse, 8 breech and 17 Caesarean sections (LSCS).

	Sensory threshold (mA)					
	Lower anal canal		Mid anal canal		Upper anal canal	
Most of delivery	Immediate post-partum	6 mo post-partum	Immediate post-partum	6 mo post-partum	Immediate post-partum	6 mo post-partum
Normal	6(2–14)*+	5(3–11)	6(2–10)*+	4(2–7)	7(3–25)*+	5(2–7)
Forceps	7(3–12*+	5(2–10)	6(3–25)*+	5(2–8)	10(3–25)*+	5(2–23)*
LSCS	5(4–9)	4(2–6)	5(3–8)	3(2–9)	5(3–12)	3(2–13)
Ventouse	6(2–10)	5(3–5)	5(2–10)	4·5(2–7)	5(2–25)	5(3–6)
Breech	6(4–12)*+	4·5(3–7)	5·5(3–10)	4(2–10)	6(3–9)	4(2–12)
Controls	4(3–9)		4(3–7)		4(3–10)	

Results are median with range in parentheses $^+P<0·05$ cf controls, $^*P<0·05$ cf LSCS, Mann–Whitney *U* test

The results show initial impaired sensation after normal and forceps deliveries but the only remaining impairment by 6 months is in the upper anal canal in the forceps group compared with LSCS This may contribute to the later development of incontinence. Ventouse delivery caused no significant changes in sensation and it may therefore be preferable to forceps delivery

Successful treatment of human colorectal cancer xenografts using early photodynamic therapy

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Conventional 'delayed' photodynamic therapy (PDT) is a two-step procedure. A photosensitizing agent, usually haematoporphyrin derivative (HPD) is administered and after a delay of 1–3 days the tumour is irradiated with red light to coincide with the peak tumour/normal tissue ratio. Ths purpose of this study was to determine whether 'early' PDT, timed to coincide with peak circulating HPD levels rather than peak tumour HPD levels, could cause tumour destruction

Nude mice bearing COLO320 DM tumour xenografts were sensitized by intraperitoneal injection of 10 mg/kg HPD. After 3–6 h, coincident with the peak serum HPD level, animals were irradiated with 150 J/cm^2 red light generated by a gold vapour laser.

Early PDT in six animals with tumour xenografts resulted in a growth delay (mean ± s d.) of 5·4 ± 2·5 days. The tumour doubling time in the exponential regrowth phase was 9·9 ± 1·9 days (versus 6·9 ± 1·2 days in six controls) and the time taken to reach a fixed end point size was 16·3 ± 2·9 days (versus 9·2 ± 1·9 days, controls) both $P>0·05$, Wilcoxon test). Electron microscopy studies showed destruction of the tumour vascular bed with preservation of adjacent tumour cell architecture

These findings demonstrate that early PDT retards tumour growth by a photochemically induced vascular occlusion.

Mucin metabolic labelling: with [^{35}S]sulphate and [^{3}H]glucosamine to monitor colonic metaplasia in the ileum following restorative proctocolectomy

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Colonic metaplasia and possibly dysplasia are features following restorative proctocolectomy. Change in the ratio of sulphomucin to sialomucin occurs in ulcerative colitis (UC), colorectal cancer and in ileoanal pouches. Mucin histochemistry is a relatively crude way of assessing this ratio of sulpho to sialomucin in the bowel. We have developed a radiolabelling technique using [^{35}S]sulphate and [^{3}H]glucosamine to follow this ratio in a total of five patients undergoing restorative proctocolectomy for UC. Biopsies were taken from the rectum, terminal ileum and 20 cm proximal at surgery, and repeated pre and 8 weeks postileostomy closure The radiolabelling ratios of [^{35}S]sulphomucin to [^{3}H]sialomucin were as follows: rectum 0·75 ± 0·10, distal ileum 0·43 ± 0·06, proximal ileum 1·03 ± 0·11, preclosure 0·43 ± 0·06, postclosure 0·76 ± 0·21. The expected sialomucin preponderence was found in the colitic rectums, which differed from the ileums ($P<0·02$) There was also a highly significant difference between the proximal and distal ileum ($P<0·001$), which was not apparent on the standard high iron diamine/alcian blue staining. Pre-ileostomy closure, the ratio fell to the distal terminal ileal values. Postclosure, these rose and approached the colitic rectal values.

We conclude that this differential radiolabelling technique is a highly sensitive index of mucin changes which can be used to monitor colonic metaplasia following restorative proctocolectomy.

Adrenergic control in the internal anal sphincter is abnormal in patients with idiopathic faecal incontinence

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Microscopic studies of the internal anal sphincter (IAS) have shown muscle fibre atrophy and fibrosis in idiopathic faecal incontinence (IFI). To assess the muscle pharmacology and innervation, we studied the response of resected muscle to exogenous noradrenaline and electrical field stimulation (EFS).

Circumferential muscle strips from eight patients (age 39–79 years, seven female, one male), with IFI undergoing postanal repair and five control patients (age 44–74 years, two female, three male) undergoing abdominoperineal resection for carcinoma were studied. Patients with IFI had pre-operative anorectal physiology. Responses to noradrenaline (10 nM–0·1 mM) and EFS (1–32 Hz, 0·5 ms, 60–150 V) were studied in organ baths, under auxotonic conditions.

The contraction–response curve to noradrenaline in patients with IFI was significantly different from controls at every concentration tested ($P<0·001$) There was no correlation between resting anal pressure and the contractile response (EC$_{50}$) to noradrenline in the IFI group. With EFS there was an initial contraction prior to relaxation in four controls: this contraction was blocked by phentolamine. None of the IFI group showed this contraction ($P<0·01$). Relaxations in both groups were resistant to atropine, phentolamine and propanolol, indicating that they were non-adrenergic, non-cholinergic in nature.

Patients with IFI show decreased sensitivity to noradrenaline which is an important neurotransmitter in sympathetic nerves supplying the IAS. The response to EFS and phentolamine shows that the excitatory adrenergic innervation is also abnormal, demonstrating that the relationship between the sympathetic innervation and non-adrenergic, non-cholinergic control is disturbed.

Nocturnal leakage is related to high pressure pouch waves following restorative proctocolectomy

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Restorative proctocolectomy is occasionally associated with faecal leakage, especially at night This has been seen in patients with high pressure pouch waves. We have investigated anal canal and pouch pressures by compressed, computerized ambulatory monitoring in ten controls (C), ten continent pouch patients (CON) and five with nocturnal leakage (INC) over prolonged periods (13·5 h median, range 7–25) to determine changes in pressure profiles associated with leakage. Average daytime anal pressures were similar in all groups, given as cmH$_2$O, median with range in parentheses: C=66 (37–121), CON=54·5 (47–73), INC=54·7(47–73) but controls had higher nocturnal pressures, $P<0·01$, C=24 (16–42); CON=16 (6–28); INC=10 (0–62) Nocturnal pressure was significantly lower versus daytime pressures in all groups; $P<0·001$. High pouch pressure waves were seen in four incontinent and one continent patient. These were mirrored by anal pressure increases Pouch pressure 113 (74–121) approximated anal pressure 114 (104–131) during the day and at night 89 (40–138) versus 97 (36–132). At night, pouch pressure exceeded anal pressure on 25 per cent of occasions; but not in the daytime, nor in the continent patient with high pressure waves Average pouch wave frequency was five per hour. In conclusion, there is a marked drop in anal pressure during sleep in all individuals. Pouch pressure waves are associated with leakage, but only at night does the pouch pressure ever exceed the anal pressure response.

Somatostatin receptors in human colorectal cancer

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Somatostatin is a powerful inhibitory peptide which has important cytostatic properties on some malignant cell lines, probably by receptor-mediated activation of tyrosine phosphatase. We have developed an assay for membrane-bound somatostatin receptors (SR) utilizing $[\mathrm{I}^{125}]$somatostatin 14 as ligand and rat cerebral cortex as positive control. The aim of the study was to investigate SR expression by colorectal cancer (CRC), which has not been demonstrated previously

Specimens of CRC and 'normal' colonic mucosa were collected at operation and snap frozen in liquid nitrogen. Tissue was homogenized, membranes prepared and a multi-point binding assay performed The dissociation coefficient (K_d) and receptor density (B_{max}) were calculated by Scatchard analysis, the B_{max} being expressed in relation to the protein concentration of the membrane preparation.

	Rat cortex ($n=5$)	Mucosa ($n=12$)	Tumour ($n=12$)
B_{max} (fmol/mg protein)	213 (167–319)	734 (278–3460)*	2991 (1196–10 826)*
K_d (nM)	0·85 (0·84–0·92)	132 (73–337)	145 (84–204)

Results are median with range in parentheses, * $P<0·05$

Thus, SR expression is ubiquitous in CRC although the affinity is 100 times lower than in the 'classical' (rat cortex) SR. The receptor density is also much higher These data support the potential of pharmacological doses of somatostatin analogues in CRC.

Ileal pouch adaptation and anal canal recovery after restorative proctocolectomy

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When intestinal continuity is restored after restorative proctocolectomy (RP), bowel frequency diminishes in the first few weeks, any changes thereafter being more subtle. Our hypothesis was that adaptation of the reservoir and recovery of the sphincter were responsible for these changes.

We measured the pressure profile and threshold electrosensitivity of the anal canal, the capacity and compliance of the reservoir and performed continuous ambulatory manometry in 20 patients before RP and 3, 7 and 12 months after operation.

Bowel frequency, expressed as median number of times per day with interquartile range in parentheses, decreased from 8 (7–9) at 3 months to 5 (4–6) at 7 months ($P<0·01$) and 4 (3–6) at 12 months. The resting anal pressure was 79 cmH_2O (70·3–89·0) before operation and 68 cmH_2O (50·8–87) at 3 months ($P=0·004$) but had recovered to the pre-operative value in 18 of 20 patients by 12 months. The MTV increased from 190 ml (140–220) at 3 months to 285 ml (207–355) ($P<0·01$) at 12 months and the pouch compliance increased from 9·1 ml/cmH_2O (6·9–9·92) at 3 months to 12·5 ml/cmH_2O (9·15–14·9) at 12 months ($P=0·028$). The 'recto'-anal inhibitory reflex was present in 3 of 20 patients at 3 months, 10 of 20 patients at 7 months and 19 of 20 patients at 12 months ($P<0·01$). Intermittent equalization of anal and pouch pressures during ambulatory manometry was present in 1 of 20 patients at 3 months, 8 of 20 at 7 months and 17 of 20 at 12 months.

In conclusion, significant adaptation of the pouch and recovery of the anal canal occurs after RP

Effect of failed laser angioplasty on limb blood flow

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Percutaneous laser angioplasty (PLA) may have a role in the treatment of long peripheral occlusions. However, there is concern that when this technique fails, limb perfusion may be compromised. To test this hypothesis, a new method of isotope limb blood flow (LBF) measurement[1], was used to assess limb perfusion in 19 patients undergoing PLA, before and 1 month after treatment.

Limbs with femoro-popliteal occlusions, 23 in number, ranging in length from 3–35 cm (median 8 cm) were treated by PLA using an Nd-YAG laser and sapphire-tipped optical fibre. Primary angiographic success was achieved in 19 lesions of which six reoccluded within the first month, and 13 remained patent with relief of symptoms. Urgent surgery was not required in the four technical (1°) failures.

	LBF (ml per 100 ml tissue per min)			95% confidence intervals
	Pre PLA	Post PLA	Change	
1° failures ($n=4$)	4·3±1·5	3·7±1·2	−9·4%	(−55·2–36·5%)
Reocclusions ($n=6$)	4·4±0·7	3·5±0·3	−18·6%	(−46·1–9·0%)
Patent ($n=13$)	4·4±2·1	9·1±3·5	+131·5%	(77·8–185·3%)

Results are given as means±s.e.m. Normal LBF=10 ml per 100 ml tissue per min

In conclusion, we have demonstrated a small decrease in limb perfusion following technical failures, and a greater decrease following early reocclusions, despite no subjective deterioration in these patients' symptoms.

1. Parkin A, Robinson PJ, Wiggins PA *et al.* The measurement of limb blood flow using technetium-labelled red blood cells. *Br J Radiol* 1986; **59**: 493–7.

Efficacy of Stanozolol in the treatment of lipodermatosclerosis

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Lipodermatosclerosis (LDS) occurs as a result of venous hypertension and often progresses to ulceration. It is postulated that pericapillary fibrin 'cuffs' cause an oxygen diffusion block resulting in local hypoxia The anabolic steroid, Stanozolol, enhances fibrinolysis and has been advocated for the treatment of LDS to prevent ulceration A double-blind placebo controlled randomized trial was undertaken to assess the efficacy of Stanozolol in this condition. Treatment (5 mg Stanozolol or placebo b.d.) was given for 6 months. The liposclerotic skin was measured and photographed monthly. Transcutaneous oxygen (TcpO_2) measurements were recorded at 3 monthly intervals.

A total of 60 patients were admitted to the trial. Nine patients (11 limbs) were dropped because of non-compliance or side-effects Seventy-nine limbs were assessed for a period of from 9 months to 2 years.

		Area of LDS (cm^2) at		
Treatment	n	0 mo	3 mo	6 mo
Stanozolol	39	103 (53–191)	81 (30–206)	64 (31–137)
Placebo	40	109 (61–204)	88 (45–183)	98 (48–174)

Results are median with interquartile range in parentheses

There was no significant improvement in the TcpO_2 in either group. Using multivariate regression analysis, the area of LDS showed a decrease in the Stanozolol group over 6 months ($P=0·016$). There was no change in the placebo group ($P=0·51$) Side effects in the Stanozolol group were significantly more common than in the placebo group ($P<0·02$, χ^2 analysis). None of the limbs which had not previously ulcerated developed ulcers Eleven of the limbs with a history of ulcers re-ulcerated after the period of treatment. There was no significant difference between the treatment and placebo groups ($P<0.6$, χ^2 analysis).

Stanozolol effects a decrease in the area of lipodermatosclerosis but whether this prevents ulceration has not been established.

Platelet deposition on mesothelial-seeded Dacron as femoral artery grafts

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Previous work suggests that mesothelial seeding of Dacron aortic grafts in dogs increases the cellular lining of the graft and local prostacyclin production. It was investigated whether the technique leads to a reduction in platelet deposition when applied to femoral artery grafts.

Thirty female greyhounds underwent bilateral femoral artery replacement with 6 cm lengths of 6 mm internal diameter knitted Dacron (Meadox Microvel) One graft was seeded with autologous mesothelial cells prepared by collagenase digestion of omentum obtained under the same anaesthetic. At 5 days and 8 weeks, autologous platelets labelled with indium-111 were infused and graft uptake measured over 5 days using a probe and ratemeter. The daily rise in the ratio of graft to blood radioactivity was expressed as the thrombogenicity index (TI) One week after the second platelet study each graft was removed, the lumen photographed and computer-assisted planimetry applied to measure the percentage of graft surface free from thrombus

Early TI (mean ± s e m.) at 0·88 ± 0·25 in seeded grafts was not significantly less than 0·95 ± 0·25 in controls. At 2 months when cell cover should have developed there was still no significant difference between the TI of 0·47 ± 0·08 in seeded grafts and 0·38 ± 0·08 in controls. The decrease in TI at 2 months was significant only in unseeded grafts ($P = 0{\cdot}05$, Wilcoxon test). Similarly the percentage thrombus-free area at 32·5 ± 4·0% in seeded grafts did not differ significantly from 30·8 ± 4·7% in unseeded controls

In contrast to mesothelial seeded Dacron implanted in the aorta, mesothelial seeding confers no effective antiplatelet activity on Dacron femoral artery grafts

Laser vascular anastomosis – a comparison of argon and ND-YAG lasers for a new vascular technique

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Laser vascular anastomosis (laser welding) is currently under evaluation in medium-sized vessels. The main potential benefit is improved anastomotic healing with minimal foreign body reaction. Tissue fusion is achieved by the thermal effect of laser energy but diffusion of heat beyond the anastomosis may produce thermal damage and vessel constriction. This study compared the mechanical strength and degree of constriction of welds produced by two different laser wavelengths Four hundred porcine coronary arteriotomies were repaired *in vitro* Anastomotic bursting pressure was measured by infusion of saline under pressure. Vessel constriction was assessed using a constant pressure flow rate model (ratio pre/post repair).

	Power density (W/cm^2)	Burst pressure (mmHg)	Flow rate (%)
Argon	5·7	280 ± 22	85 ± 3
Nd-YAG	105	273 ± 30	64 ± 7
Control		> 500	93 ± 2

Results represent optimal welds compared sutured controls (mean ± s.e)

Burst pressures showed no significant difference between lasers but the argon produced less constriction ($P < 0{\cdot}01$, one-way ANOVA). All argon welds showed burst pressures > 200 mmHg with constriction only minimally greater than controls ($P = 0{\cdot}05$). In conclusion, vascular repairs produced by laser can withstand suprasystolic pressures and demonstrate minimal constriction. In both respects the argon laser is superior. An *in vivo* study employing this laser for definitive anastomoses is in progress.

Comparative trial of ascending phlebography versus Duplex ultrasonography in the diagnosis of deep venous thrombosis

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A consecutive series of 70 patients (93 limbs) referred for ascending phlebography for suspected deep venous thrombosis of the lower limb were examined by Duplex ultrasonography. Duplex scans were performed in the supine position. Assessment of the iliac, common, profunda and superficial femoral, long saphenous, popliteal, calf stem and sinusoidal vessels was carried out. Venous compression, flow detection and flow augmentation were the main criteria for Duplex diagnosis of thrombus. Phlebography failed in three limbs, and 90 limbs were thus available for comparison.

Thrombi 90 limbs	Phlebo positive	Duplex positive	False positive	False negative	Duplex sensitivity (%)	Duplex specificity (%)
Iliac	12	13	1	0	100	98·6
CFV	20	21	1	0	100	98·6
SFV	27	28	2	1	96·3	96·8
Popliteal	25	25	0	0	100	100
Calf	43	40	4	7	83·7	91·5

CFV, common femoral vein; SFV, superficial femoral vein

No thrombus was detected in 43 limbs (47·7 per cent) on X-ray. Of these, 40 (93·0 per cent) were normal on Duplex. Two false positives were related to tenderness in the limb and one to post-thrombotic change.

Forty-seven limbs (52·2 per cent) had thrombi present on X-ray. Forty-one were correctly identified by Duplex (87·2 per cent), whilst six false negative scans were in patients with isolated calf thrombi. Duplex had 100 per cent sensitivity for the femoropopliteal thrombi, but only 11 out of 17 isolated calf thrombi (64·7 per cent) were correctly diagnosed by Duplex. Duplex can thus reliably diagnose thrombi in the proximal axial vessels, although 35 per cent of isolated calf thrombi escaped detection.

Healing failure of symptomatic carotid plaques following an ischaemic neurological event

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Carotid plaque haemorrhage is believed important in the production of stroke. It has been reported that haemorrhage into the plaque is temporally related to stroke and that it undergoes a healing process Multiple plaque sections from 44 symptomatic (Sym) and 8 asymptomatic (Asym) patients were studied. Sections were stained with haematoxylin and eosin (HE), Pearl's Prussian blue, Van Gieson and Martius scarlet blue. Plaque constituents were quantified by planimetry and expressed as a percentage of plaque content.

Haemorrhage occupied < 2% of Sym and Asym plaque content Sym and Asym plaques were composed mainly of fibrous (F) material, Sym containing significantly less than Asym, (66 ± 11 per cent versus 88 ± 15 percent, $P < 0{\cdot}05$) The dominant non-fibrous material was a pink staining (HE) material mixed with cholesterol which was greater in Sym (27 ± 5 per cent) than Asym (7 ± 2 per cent) ($P < 0{\cdot}05$). Plaques associated with multiple (> 5) cerebral events (F = 62 ± 13 per cent) did not differ from those with single events (F = 68 ± 23 per cent). Plaques associated with an event-surgery interval of < 1 week (F = 69 ± 15 per cent) did not differ from those with an event-surgery interval of 10 or more weeks (F = 73 ± 15 per cent)

The important Sym plaque component is not haemorrhage but an amorphous substance mixed with cholesterol and this material does not undergo a healing process following an ischaemic neurological event

Venous valve replacement: a new technique

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Correction of post-thrombotic deep vein reflux necessitates valve replacement Currently available techniques have had limited success, but incompetence and thrombosis have precluded their widespread use Using the canine hind limb, we have used autogenous femoral vein wall to produce a size-matched valve mechanism[1] The femoral vein is mobilized and divided, and an external jugular vein graft interposed between the two ends to lengthen the vein. The femoral vein is then intussuscepted and secured to produce two cusps.

Contribution of participation in randomized clinical trials with informed consent to psychiatric morbidity

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A study by Fallowfield *et al*[1] to identify psychosocial morbidity associated with the diagnosis and treatment of early breast cancer, found high rates of anxiety and depression one year later, regardless of type of operation.

The sample comprised 101 women who had not expressed strong preference for treatment, randomized to treatment following informed consent. The major criticism[2] of this study was that women who 'surrender' autonomy for decision making in this way experience different problems from women treated outside the setting of a clinical trial

The present study of 269 women was designed to meet the criticisms of the earlier one, by recruiting women from surgeons 'favouring' one approach or the other. Measuring instruments were identical for both studies, enabling direct comparison of data.

Of women who had a mastectomy following randomization, 26 per cent had an anxiety state, compared with 27 per cent in the current study The rates for women following breast conservation were 31 and 27 per cent respectively. Of women in both studies who had mastectomy, 21 per cent were depressed, while rates for women following breast conservation were 27 and 19 per cent respectively. None of these differences are statistically significant. There is no evidence that randomization with informed consent is associated with adverse psychosocial consequences, and the prime determinant of morbidity is the diagnosis rather than the treatment.

1 Fallowfield JL, Baum M and Maguire GP. Effects of breast conservation on psychological morbidity associated with diagnosis and treatment of early breast cancer. *Br Med J* 1986, **293**: 1331–4.
2. Milner PC and Nicholl JP. Effects of breast conservation on psychological morbidity. *Br Med J* 1986, **293**: 1568.

Limitations of fine needle aspiration cytology for the diagnosis of mammary cancer

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Fine needle aspiration cytology (FNAC) is of documented value in the assessment of isolated breast lumps. We have prospectively used FNAC as a test of the presence of neoplasia in 2000 consecutive referrals to our breast clinic, and compared our results to the final histological findings. There were 264 malignancies in this series of which 222 (84 per cent) were diagnosed by FNAC. Positive identification of frankly malignant cells was made in 65 per cent of these, with 19 per cent reported as suspicious of malignancy. Of specimens, 1509 were declared benign, but 38 of these proved to be malignant on final diagnosis, giving an overall false negative rate of 2·5 per cent.

Pathology	Total No. of patients	False negatives	% of total
Ductal	233	27	11·6
Lobular	23	9	39·0
In situ	3	3	100·0
Medullary	4	0	0
Lymphoma	1	0	0

There were 11 (0·6 per cent) false positive diagnoses in this study, 8 of which were reported as suspicious, the remainder frankly malignant. This study demonstrates the accuracy of FNAC in the pre-operative assessment of primary mammary neoplasia. Furthermore, our results suggest that a negative FNAC result should be followed up by histological assessment in suspicious cases, as lobular and *in situ* patterns of carcinoma are particularly associated with false negative results.

Magnetic resonance imaging of the axilla in the management of breast carcinoma

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This prospective study assesses the efficacy of magnetic resonance imaging (MRI) in the evaluation of axillary node status and disease staging in patients with breast carcinoma.

Twenty-eight patients with biopsy-proven breast carcinoma were studied by MRI. Images were obtained in coronal and axial planes using T1 and T2 weighted pulse sequences. MRI has advantages over other imaging techniques in that it not only provides excellent soft tissue detail but also has the ability to characterize tissue and in theory may be able to demonstrate non-enlarged metastatic lymph nodes. All the patients proceeded to either Patey mastectomy or lumpectomy combined with axillary sampling within 10 days of the MRI scan.

The results of MRI were correlated with the histopathological findings. There were 16 true negative MR studies, 9 true positive studies and 1 false positive study. In 2 cases no nodes were identified in the resected specimen.

A protocol for MR investigation and interpretation is proposed which could select out patients with equivocal appearances where axillary sampling would remain necessary. Such a protocol would have reduced the number of cases requiring node sampling in this study by >60 per cent while retaining 100 per cent accuracy.

Local recurrence after treatment of early breast cancer – a non-problem

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Loco-regional recurrence after treatment of early breast cancer by conservative surgery and radiotherapy has recently been reported to be as high as 33 per cent[1] Such high recurrence rates might discourage the practice of conservation treatment.

Associated distant disease alters the therapeutic and prognostic significance of local recurrence. We have investigated the pattern of local and distant recurrence after treatment in 145 women with early breast cancer. All women underwent wide local excision, axillary clearance and breast irradiation.

There were 13 cases of locoregional recurrence (breast 10, axilla 2, supraclavicular fossa 1) and 19 cases of recurrent distant disease Disease free survival at seven years was 83 per cent (life table analysis) Analysis of isolated loco-regional recurrence revealed only four cases within the breast and one axillary recurrence without coexistent, preceding or subsequent distant disease (isolated local disease free survival = 96·5 per cent). All local recurrences were amenable to further local treatment. Distant recurrence was found in 19 women (distant disease free survival = 88·3 per cent) and the majority of first recurrences (68 per cent) occurred at distant sites. All breast cancer deaths ($n = 14$) occurred in women with recurrent distal disease.

Isolated loco-regional recurrence was a rare event in this series and did not pose a significant clinical problem.

1. Locker AP, Ellis IO, Morgan DAL *et al.* Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. *Br J Surg* 1989, **76**: 890–4

Predictive effect of oestrogen receptors for long term survival in patients with operable breast cancer

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Ten years ago, we were one of the first groups to observe the short term prognostic significance of oestrogen receptor (ER) in patients with primary breast cancer[1]. We now report the long term follow-up of this study.

Patients (708) with stage I and II breast cancer treated by mastectomy without adjuvant systemic therapy between 1975 and 1981 had their oestrogen receptor status determined by a ligand-binding competitive inhibition assay. Patient details and cause of death were recorded prospectively and survival data was analysed by life table methods.

The median survival for the 386 (55 per cent) patients with ER-positive tumours was 60·7 months compared to 62 months for the 322 (45 per cent) in the ER-negative group although the overall survival was significantly better for the ER-positive patients ($\chi^2 = 6·69$, $P < 0·009$). Unlike the earlier report, ER did not affect survival in stage I disease but, in patients with nodal involvement, median survival was

54 months for ER-positive compared with 40 months for ER-negative patients ($\chi^2=8\cdot8$, $P<0\cdot003$).

Although, after long-term follow-up, ER remains a prognostic factor in patients with operable breast cancer this is now seen to be due to an improvement in short term mortality. Stage II patients with ER-negative tumours continue to have a poor prognosis but the predictive value in stage I disease no longer holds.

1 Cooke TG, George WD, Maynard P, Griffiths K Shields R. Oestrogen receptors and prognosis in early breast cancer. *Lancet* 1979; i: 995

Automated quantification of immunocytochemically localized oestrogen receptors in breast cancer

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Immunocytochemical assay of oestrogen receptor (ERICA) in human breast cancer provides a rapid result. Good correlation has been reported between the percentage of tumour cells staining positive and response to endocrine therapy[1]. However immunohistology introduces an element of subjectivity to this measurement We have compared quantification of specific ER staining by manual procedures using optical microscopy with a computer assisted image analysis system (CAS 100, Becton Dickinson).

Frozen sections of 92 samples were stained using an immunoperoxidase (ERICA) kit incorporating a monoclonal antiserum (H222) to visualize nuclear human ER Fifty-four patients were treated with endocrine therapy and were assessable for response.

There was a highly significant relationship between CAS and manual assessments ($r=0\cdot919$, $P<0\cdot01$). There was a significant association between CAS assessment and hormone sensitivity.

	ER positive cells (%)		
Clinical assessment	0	1–40	>40
Response	0	8	8
Static	2	3	6
Progression	14	7	1

$\chi^2=22\cdot5$, 4 d.f.; $P<0\cdot001$

Automated image analysis offers a reliable quantification of ER which may be carried out by a technical officer It provides less opportunity for subjective influences in scoring. CAS assessment of ER is a good predictor of hormone sensitivity.

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Aspiration cytological diagnosis of breast lesions by nuclear DNA content and morphometry

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There is increasing use of fine needle aspiration cytological diagnosis of breast lesions. However this requires considerable expertise on the part of the pathologist. Image cytometry provides an objective and reproducible means of estimating nuclear DNA and studying nuclear morphometry

Fine needle aspirates of 148 breast lesions were examined by static cytometry (CAS 100 image analysis system) and divided to diploid and aneuploid/tetraploid. Diploid lesions were further analysed measuring a number of morphometric variables

	DNA ploidy	
Final diagnosis	Diploid	Aneuploid/tetraploid
CA	28	66
Benign	48	6

Sensitivity = 70 per cent; specificity = 91 per cent

Discriminant analysis of 51 diploid lesions was performed incorporating ten morphometric variables, DNA index and patient age. When these results were combined with the above information the following was obtained.

	Final prediction ($n=123$)	
Final diagnosis	CA	Benign
CA	75	3
Benign	8	37

Sensitivity = 96 per cent, specificity = 90 per cent

This level of sensitivity is higher than that usually reported by experienced cytologists for breast lesions These measurements may be used to aid cytologists in the reading of fine needle aspirates of breast lumps and with further development may replace the cytologist.

Causes of suppression of baroreflex activity in injured man

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Our finding that injury causes prolonged suppression of baroreflex activity in man has been reported to this society We have studied the mechanism of this derangement of a critical homeostatic reflex in order to shed light on the significance of this and other systemic responses to injury. The effects on the baroreflex of three components of injury, namely blood loss, mental stress and stimulation of nicoceptors (pain receptors), were studied in healthy volunteers using the neck chamber method

The loss of 500 ml blood had no effect on baroreflex sensitivity. Median baroreflex sensitivity was 3·3 (range −0·1 to 18·5) ms mmHg^{-1} before, and 3·5 (0·4 to 14·7) ms mmHg^{-1} 30 min after venesection ($n=12$, P n.s., Wilcoxon signed rank test)

Reflex heart slowing in response to 40 mmHg neck suction was similar before and during the performance of mental arithmetic (MA), an accepted mental stress. control 182 (104 to 402) ms, MA 135 (28 to 480) ms, $n=7$, P n s, Wilcoxon rank sum test

Baroreflex sensitivity was little changed by MA (difference 0·36, (−0·9 to 1·8) ms mmHg^{-1}, $n=4$) Further, the stress of admission to hospital for day case surgery had no significant effect on baroreflex sensitivity: patients ($n=5$) 4·6 (0·66 to 9·67) ms mmHg^{-1}, controls ($n=22$) 3·7 (0·09 to 15·5) ms mmHg^{-1}, P n s., Wilcoxon rank sum test.

Nociceptors were stimulated by the inflation of a thigh cuff above systolic blood pressure for 10 min This stimulation reduced reflex heart slowing in response to 46 mmHg neck suction from 237 (43 to 540) ms to 122 (27 to 630) ms, ($n=10$, $P<0\cdot05$, Wilcoxon signed rank test)

These findings suggest that nociceptive stimulation causes changes in baroreflex function similar to those produced by injury while modest blood loss and mental stress have no such effect This implies that tissue injury mediates this systemic effect of injury Blockade of these neural signals may have an early role in the treatment of injury.

Trypsinogen activation peptide: a prediction of pancreatic necrosis in acute pancreatitis

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Using an antibody which will only bind the C-terminal end of trypsinogen activation peptide (TAP) a radioimmunoassay has been developed which is capable of quantifying the amount of active trypsin without giving false positive results due to the binding of inactivated trypsinogen Since trypsinogen activation is thought to play a pivotal role in the production of severe acute pancreatitis, concentrations of TAP should correlate with disease severity We have previously reported the use of on-admission urinary TAP concentrations to distinguish mild from severe disease[1] and have not measured TAP concentration in peritoneal fluids. The mean TAP concentrations in nine patients with proven necrosis, five with complicated attacks but without proven necrosis and six with uncomplicated attacks were 6·2 nM (range 0·69–21 nM), 0·81 nM (range 0–3 nM) and 0·1 (range 0–0·4 nM) respectively Significant difference in TAP concentrations were found between patients with necrotizing and complicated disease

($P<0{\cdot}02$ Mann–Whitney U test), and necrotizing and uncomplicated disease ($P<0{\cdot}002$ Mann–Whitney U test). Although numbers are small these results provide support for the theory that intrapancreatic zymogen activation plays an important role in the production of acute pancreatitis and suggest that concentrations of TAP within peritoneal fluid may provide useful discrimination between necrotizing and other forms of acute pancreatitis

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Evidence of circulating α-2 macroglobulin-protease complexes in acute pancreatitis

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During severe acute pancreatitis, plasma levels of the antiprotease α-2 macroglobulin (α2M) fall, particularly in severe attacks, probably because α2M forms complexes with active proteases which then stimulate specific receptor-mediated endocytosis by macrophages. However, proteolytic activity has not been demonstrated in plasma

Twenty-seven patients with acute pancreatitis were investigated for the presence of α2M-protease complexes using a newly developed sandwich ELISA assay which utilized a monoclonal antibody specific to complexed α2M. Plasma samples were collected daily for 8 days Total α2M, 1-protease inhibitor and C-reactive protein were measured using nephelometry. Nineteen patients who had an uncomplicated attack were classified as mild, and eight attacks complicated by multi-organ failure or a pancreatic pseudocyst were classified as severe (four deaths).

In the severe groups there were higher levels of α1M-protease inhibitor, and C-reactive protein Total α2M was lower in severe patients but the proportion of complexed α2M was high.

	Total α2M (g/l)			Complexed total α2M (%)		
	Day 1	Day 4	Day 8	Day 1	Day 4	Day 8
Severe	1·2	1·07	1·17	3·6	3·5	2·9
	n.s.	*	n.s.	*	n.s.	n.s.
Mild	1·5	1·51	1·83	0·78	1·2	0·47
	normal >1·3 g/l			normal <0·7%		

* $P<0{\cdot}05$, Mann–Whitney U test. n.s., not significant

This study shows that α2M-protease complexes were more prevalent in severe acute pancreatitis and present during the initial 8 days of the attack. The complexes are biologically active (possessing peptidase activity) and may play an important role in the pathogenesis of the 'septic' illness which is frequently a feature of severe pancreatitis.

Abrogation of tumor necrosis factor (TNF) toxicity in the murine model by taurolidine: support for synergism of TNF with endotoxin

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The application of recombinant tumor necrosis factor (TNF) in the treatment of solid tumours has been limited by life threatening toxicity Recent evidence has suggested that a marked synergism between endotoxin (at the picogram level) and TNF may contribute to this toxicity[1]. We postulated that the use of the anti-endotoxin taurolidine, may reduce TNF toxicity by interfering with this synergy and thus permit administration of greater amounts of TNF

C57/BL6 mice ($n=120$) received toxic doses (12 μg/mouse i.v.) of TNF Four groups were studied: group 1, TNF alone; group 2, TNF followed immediately by 200 mg/kg taurolidine i.v.; group 3, 200 mg/kg taurolidine i.v. 30 min before TNF; group 4, 200 mg/kg taurolidine i.p. 45 min before TNF.

Group	Mortality at 5 days (%)
1	46·6
2	40·0
3	11·1*
4	50·0

* $P<0{\cdot}005$, χ^2 analysis

These data demonstrate a significant reduction in *in vivo* toxicity of TNF and support the concept of synergism between TNF and endotoxin The clinical application of taurolidine in patients receiving TNF would appear justified However, this will depend on taurolidine not interfering with TNF anti-tumour activity These experiments are now in progress.

1. Rothstein JL, Schreiber H. Synergy between tumor necrosis factor and bacterial products causes haemorrhagic necrosis and lethal shock in normal mice. *Proc Natl Acad Sci USA* 1988; **85**: 607–11.

Mediation by thromboxane of the white blood cell activation induced by ischaemia

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Indirect evidence exists that the reperfusion of ischaemic tissue activates white blood cells (WBC). Thus, reperfusion injury is prevented by making animals leucopaenic or by inhibiting ischaemia induced thromboxane (Tx)A_2 generation. This study tests directly whether ischaemia and reperfusion activates neutrophils as measured by their oxidative burst, and secondly whether Tx mediates this event. Anaesthetized rats ($n=48$) underwent 4 h bilateral hindlimb tourniquet ischaemia followed by 15 min reperfusion. At 5 and 15 min of reperfusion, plasma TxB_2 levels increased to 2750 ± 740 pg/ml and 3125 ± 995 pg/ml respectively, higher than the sham control ($n=12$) value of 370 ± 121 pg/ml ($P<0{\cdot}05$) In untreated ischaemic controls ($n=18$) the intracellular H_2O_2 production of circulating neutrophils, as assayed flow cytometrically by dichlorofluorescein oxidation, increased from a pre-ischaemic value of 133 ± 13 to 251 ± 17 and to 206 ± 21 mean fluorescence units at 5 min and 15 min of reperfusion ($P<0{\cdot}05$). Neutrophils isolated from separate blood samples at each time point were treated with phorbol myristate acetate (PMA) 10^{-7}M and showed an enhanced response to PMA, relative to pre-ischaemic activity ($P<0{\cdot}05$). Pretreatment of animals with the Tx receptor antagonist SQ29,548,2.2 mg/kg intravenous bolus and 2·2 mg kg^{-1} h^{-1} ($n=18$) did not affect plasma Tx levels at baseline or following ischaemia but prevented the ischaemia induced increase in neutrophil H_2O_2 production and enhanced response to PMA stimulation. These data indicate that ischaemia leads to neutrophil activation and enhanced neutrophil H_2O_2 production in response to a second activating stimulus; both events are mediated by thromboxane

Mediation of postischaemic renal failure by neutrophils

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Neutrophils (PMN) are central mediators in myocardial and skeletal muscle ischaemic-reperfusion injury. This study tests whether PMN mediate postischaemic renal injury Anaesthetized rats underwent right nephrectomy and 45 min of left renal pedicle clamping or sham clamping. In untreated ischaemia rats ($n=13$), 5 min after reperfusion, renal artery blood flow was 67 and 59 per cent of preclamping values at 1 and 5 min of reperfusion compared to 111 and 120 per cent at comparable time points in sham animals ($P<0{\cdot}05$). At 24 h, creatinine levels were 4·6 ± 0·3 mg/dl, relative to 0·9 ± 0·05 mg/dl in sham animals ($P<0{\cdot}05$), the weight of the left (L) ischaemic kidney relative to the right (R) normal kidney was 121 per cent compared to 95 per cent in sham animals ($P<0{\cdot}05$); and renal histology showed acute tubular necrosis (ATN). Neutrophil depletion by rabbit antiserum to rat neutrophils ($n=9$) (neutrophil count of 125 ± 56/mm^3 relative to 1531 ± 209/mm^3 in normal rats, $P<0{\cdot}01$) led during reperfusion to: increased renal blood flow relative to preclamping values, 174 and 158 per cent at 1 and 5 min ($P<0{\cdot}05$); reduced creatinine levels of 1·8 ± 0·2 mg/dl ($P<0{\cdot}05$); L/R renal weight of 101 per cent ($P<0{\cdot}05$); and limited ATN Control treatment with non-immune rabbit serum

($n=8$) did not provide protection and led to changes similar to untreated ischaemic controls. All parameters were unaffected in neutropenic shams ($n=4$). These data indicate that neutrophils mediate postischaemic renal injury.

Role of the cyclooxygenase pathway and hypothalamic factors in the stress response in man

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The neuroendocrine response that occurs following stress, trauma or infection initiates vital alterations within the host. Corticotropin releasing hormone (CRH), arginine vasopressin (AVP) and products of the cyclooxygenase pathway have each been proposed as possible mediators of this response. We studied the relationship between the induction of these mediators and the onset of the neuroendocrine response in healthy male volunteers receiving one of two standard provocative stimuli: (1) *Escherichia coli* endotoxin (4 ng/kg, i.v.), (2) hypoglycaemia induced by insulin, 0·15 units/kg, i.v.). Further subjects receiving these stimuli were pretreated with the cyclooxygenase inhibitor ibuprofen, 1600 mg orally. Serial measurement were made of circulating concentrations of CRH. AVP, ACTH and adrenaline. A portion of peak response data is shown (mean ± s.e.m.).

	AVP (pg/ml)	CRH (pg/ml)	ACTH (pg/ml)	Adrenaline (pg/ml)
Stimulus 1 ($n=6$)				
Basal	1·2±0·5	56±8	18±5	61±13
Peak (no ibuprofen)	3·0±0·5*	60±11	205±26*	151±35*
Peak (+ibuprofen)	1·6±0·5	65±11	43±22	76±13
Stimulus 2 ($n=6$)				
Basal	1·2±0·3*	44±4	8±0·3*	33±10*
Peak (no ibuprofen)	3·9±1·8	45±5	139±40	684±174
Peak (+ibuprofen)	4·1±1·5	53±2	129±37	917±225

* Different than the other two groups $P<0\cdot05$ by ANOVA

A sudden rise in circulating AVP (but not CRH) concentrations preceded the onset of all other responses following both stimuli. The prevention of this surge of AVP following endotoxin by ibuprofen was associated with blockade of the neuroendocrine response. These data suggest that cyclooxygenase-dependent and cyclooxygenase-independent pathways can both initiate the neuroendocrine response and that these pathways may exert their effects through the induction of AVP.

Work capacity as an indicator of risk in mildly malnourished surgical patients

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The capacity for work is shown to be correlated to undernutrition[1]. Up to 50 per cent of all surgical patients display some degree of undernutrition with an associated rise in surgical complications[2].

A preoperative test to identify the undernourished patient at greatest risk is described. A cycle ergometer integrated by computer to an indirect calorimeter has been designed. Subjects pedal against a light incremental load (20 W) for 15 min. The inability to complete the test rats (ICR), respiratory quotient RQ, oxygen consumption V_{O_2}, heart rate, and respiratory rate were collected and recorded.

Twenty undernourished patients were tested preoperatively, all were similar in body mass index, percentage body fat, hand grip strength and serum albumin values. Ten controls matched for age and sex were tested. Twelve patients developed nutrition-related postoperative complications, eight were uncomplicated.

The ICR was significantly greater in the complicated group (42 per cent) than in the other group (0% in both, $P0\cdot05$, Fischer exact test). V_{O_2} (ml kg^{-1} min^{-1} STP) was significantly greater in the complicated group (6·18, s.d. 2·98) than in the uncomplicated group (4·36, s.d. 1·15, $P<0\cdot05$ Mann–Whitney *U* test) or control (2·27, s.d. 2·21, $P<0\cdot01$ Mann–Whitney *U* test). Maximum rise in respiratory rate was significantly greater in the complicated group (9·33 s.d. 4·44) than in control (4·2, s.d. 3·2, $P<0\cdot01$ Mann–Whitney *U* test).

The results suggest that cycle ergometric exercise testing can preoperatively identify the mildly malnourished patient at greatest risk.

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2. Hill GL, Pickford I, Young GA *et al*. Malnutrition in surgical patients. *Lancet* 1977, i: 689–92.

New assessment of oesophageal body function

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Traditional oesophageal manometry, while of diagnostic value, is of little use in assessing or predicting the results of treatment. A new method of quantifying the activity of the oesophageal body is described in which oesophageal function is studied while eating a standardized solid meal, and the cumulative area under the pressure curve per minute, above the preprandial end-expiratory baseline pressure, is calculated. Endoscopy and perfused manometry were used to classify patients into the following groups. Group 1, normal ($n=24$); group 2, achalasia pre-myotomy ($n=12$); group 3, achalasia postmyotomy ($n=17$), group 4, Nutcracker oesophagus ($n=13$), group 5, diffuse spasm ($n=4$), group 6, benign strictures ($n=9$).

A significant increase in area/minute during eating was observed in achalasia pre-myotomy (920±33) and Nutcracker oesophagus (440±21) when compared to normal patients (220±12) $P<0\cdot001$. The high area/minute in achalasia was due to a rise in the baseline pressure and prolonged non-peristaltic waves. Patients with strictures did not demonstrate a high area/minute during eating (170±18; $n=9$). Postmyotomy achalasia patients revealed values within the normal range (140±8).

Manometry performed while eating a solid meal represents a more physiological assessment of oesophageal function and can be used to quantify the response to therapy.

Extrinsic pathology alters oesophageal motility in the dog

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Upper airway obstruction, coronary artery disease and gallbladder dysfunction are associated with oesophageal dysmotility. The aim of this study was to determine if pathology extrinsic to the oesophagus could alter oesophageal motility. Three forms of extrinsic pathology were investigated in 20 adult dogs: (1) acute, reversible coronary artery insufficiency ($n=6$), (2) increasing upper airways resistance ($n=8$), and (3) gallbladder distension ($n=6$). The animals underwent oesophageal manometry using a per oral two-sensor, transducer tipped catheter and a solid state recorder (Synectics AB). Peristaltic wave amplitude in response to a coordinated swallow, and lower sphincter pressure (LOSP) were measured.

Pathology	Peristalsis (mmHg)	LOSP (mmHg)
Coronary insufficiency		
Controls	55·5	16·0
Ischaemia	48·6*	25·9*
Upper airways resistance		
Control	41·5	14·6
0·54 kPa l^{-1} s^{-1}	48·30	16·30
1·24 kPa l^{-1} s^{-1}	55·7	15·5
8·2 kPa l^{-1} s^{-1}	60·6*	13·9
Gallbladder distension		
Control	52·8	19·7
88 mmHg	47·5	15·4
160 mmHg	48·8	12·4
240 mmHg	46·9*	9·5*

* $P<0\cdot001$ by ANOVA

Extrinsic pathology significantly influences oesophageal motility Abnormal oesophageal manometry should not be considered in isolation. The syndromes of Nutcracker oesophagus and the hypertensive lower sphincter may indicate pathology elsewhere. Our findings provide further evidence of an association between biliary disease and reflux oesophagitis.

Oesophageal emptying and dysmotility in Barrett's oesophagus

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Dysphagia has been reported in some patients with Barrett's oesophagus who do not have a peptic stricture or other obstructive lesion. The aim of this study was to evaluate the emptying and motility in Barrett's oesophagus and compare this with that in reflux oesophagitis without Barrett's abnormality. Twenty patients with Barrett's oesophagus and 20 with reflux oesophagitis with comparable age group underwent oesophagoscopy, oesophageal manometry and oesophageal scintigraphy in the upright and supine positions. The mean length of Barrett's oesophagus was $7{\cdot}5 \pm 2{\cdot}5$ cm. The half time emptying in the upright posture was not significantly different in the two groups but in the supine position there was a significant ($P<0{\cdot}02$) delay in oesophageal emptying in the Barrett's oesophagus group The retained tracer after 150 ml of drink was significantly ($P<0{\cdot}004$) higher in the Barrett's group (median 16 per cent) compared with the oesophagitis group (median 9·0 per cent). Oesophageal manometry showed a significant ($P<0{\cdot}019$) hypotensive oesophageal sphincter and lower mean lower segment peristaltic pressure in Barrett's oesophagus. There was no correlation between dysmotility and length of columnar lined oesophagus.

It is concluded that dysphagia may result from impaired oesophageal emptying in Barrett's oesophagus in the absence of stricture and that this is associated with lower peristaltic pressure in the lower oesophageal segment.

Gastric mucosal microvascular damage in experimental gastric stress ulceration

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Acute gastric stress ulceration involves damage to the mucosal microcirculation. Prophylaxis can be achieved using H-2 receptor antagonists and prostaglandins and allopurinol. We used scanning electron microscopy (SEM) of corrosion casts of the gastric microcirculation in five groups of fasted Wistar rats to quantify the microvascular damage induced by stress and the influence of cimetidine, misoprostol and allopurinol prophylaxis. The groups were: (1) control, (2) untreated stress, (3) 50 mg/kg allopurinol p.o. three times daily before stress, (4) 10 mg/kg cimetidine i.m 1 h before stress and (5) 50 μg/kg misoprostol p.o. immediately before stress. After stress induced by restraint at 4°C for 2 h, stomachs were casted using Batson's corrosion compound, digested in 34 per cent KOH, coated with gold and scanned with an Hitachi S-520 SEM with a magnification of 500. Ten micrographs from standardized sites in each stomach, 50 per group, were coded, randomized and graded, blindly, on a scale of 0–5 (normal to severely damaged).

	Grade					
Treatment	0	1	2	3	4	5
Control	31	14	4	1	0	0
Allopurinol	6	19	10	12	3	0
Cimetidine	3	11	20	9	7	0
Misoprostol	1	5	11	19	11	3
Untreated stress	0	3	2	3	14	28

Stress significantly disrupted the gastric microcirculation ($P<0{\cdot}01$). Pre-treatment with cimetidine ($P<0{\cdot}01$), misoprostol ($P<0{\cdot}01$) or allopurinol ($P<0{\cdot}01$) significantly reduced this damage. Allopurinol and cimetidine were superior to misoprostol ($P<0{\cdot}01$). Statistics were performed using a χ^2 analysis. These results demonstrate the importance of damage to the microcirculation in stress ulceration.

Inhibition of intragastric fibrinolytic activity after a peptic ulcer haemorrhage

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There is experimental evidence that intragastric tryptic and fibrinolytic activity are increased following peptic ulcer haemorrhage with good correlation between trypsin and lysis. Inhibition of trypsin may prevent dissolution of the blood clot sealing the bleeding point on the ulcer and therefore prevent rebleeding. Aprotinin is an effective inhibitor of trypsin. The aim of this prospective study was to determine the effect of aprotinin on gastric juice tryptic and fibrinolytic activity. Seventeen patients with peptic ulcer haemorrhage were randomized to receive either aprotinin 2·4 megaunits or distilled water as a continuous intragastric infusion over a 24 h period. Hourly gastric juice aspirates were tested for pH, bile acids, trypsin and fibrinolytic activity. Statistical analysis (Mann–Whitney *U* test) was performed using the area under the curve. There were no significant differences in the gastric pH ($Z=0{\cdot}91$, $P=0{\cdot}3$), bile acid concentration ($Z=1{\cdot}27$, $P=0{\cdot}2$) or fibrinolytic activity ($Z=1{\cdot}32$, $P=0{\cdot}19$). Intragastric trypsin was significantly lower in the aprotinin group ($Z=2{\cdot}68$, $P=0{\cdot}007$). Two patients with no intragastric tryptic or fibrinolytic activity rebled compared to three patients with high activity. This data suggests that intragastric trypsin can be effectively inhibited by aprotinin, that other fibrinolytic agents, not inhibited by aprotinin, are also involved and that more than one mechanism of rebleeding may be present.

Efficacy of somatostatin in controlling postinjection sclerotherapy bleeding from varices *per se*, oesophageal ulcers and oesophagitis

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Bleeding from the varices themselves, oesophageal ulcers or oesophagitis after injection sclerotherapy is usually minor but can occasionally be massive and difficult to control. Since somatostatin (SRIF) is a safe and effective treatment for the acute variceal bleed we have evaluated its efficacy in these postinjection sclerotherapy complications.

Thirty-eight patients experienced a significant upper gastrointestinal bleed at various times after injection sclerotherapy. A significant bleed was defined as either a systemic disturbance: blood pressure <100 mmHg; pulse >100 beats/min requiring blood transfusion or the necessity to transfuse two or more units to restore the haemoglobin levels. Endoscopy revealed that 16 patients were bleeding from varices, 14 from oesophageal ulcers and 8 from oesophagitis. All patients were treated with SRIF (bolus dose of 250 μg followed by a continuous infusion of 250 μg/h) for between 2 and 7 days.

Haemorrhage was successfully controlled in all patients bleeding from oesophagitis and in 12 of the 14 bleeding from oesophageal ulcers by somatostatin infusion. In the two patients with persistent bleeding from ulcers, haemorrhage was eventually controlled by hourly bolus injections of SRIF for a period of 24 h superimposed on the continuous infusion. SRIF was also successful in controlling haemorrhage in 15 of the 16 patients bleeding from their varices.

The results of this study suggests that SRIF is a safe and effective treatment for controlling severe haemorrhage after injection sclerotherapy.

Testicular effects of tumour necrosis factor

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TNF has been implicated in the cachexia and catabolic response of chronic illness. As testicular androgens are anabolic and are depressed during chronic illness we investigated the effect of TNF on testicular androgen production. We administered rhTNF (0, 2, 4×10^5 units kg^{-1}) $(24\ \mathrm{h})^{-1}$, to 200 g male Wister rats ($n=85$) on a fixed intravenous diet. Testicular weight, histology and plasma LH, FSH and testosterone were determined at killing following TNF infusion over 1, 3 and 6 days.

	Test wt (g)	Testosterone (ng/ml)	LH (ng/ml)	FSH (ng/ml)
Day 1 TNF 0	1·20±0·03	0·80±0·39	0·42±0·12	19·5±5·2
TNF 2	1·10±0·03*	0·32±0·06	0·88±0·31	24·7±6·8
TNF 4	1·12±0·03	0·25±0·08	0·60±0·23	21·2±9·2
Day 3 TNF 0	1·21±0·04	1·07±0·50	0·24±0·08	18·5±5·6
TNF 2	1·12±0·08	0·17±0·09*	0·61±0·21	26·8±8·5
TNF 4	1·12±0·05	0·12±0·06*	0·51±0·20	19·1±2·0
Day 6 TNF 0	1·22±0·04	0·46±0·24	0·31±0·08	12·7±3·9
TNF 2	1·04±0·03*	0·09±0·03*	1·36±0·27	23·3±2·5
TNF 4	0·91±0·08**	0·05±0·02*	1·86±0·6*	33·4±7·2**

Results are means±s.e.m. *$P<0·05$, **$P<0·005$, versus control, ANOVA

TNf infusion decreased testicular weight which was noted at 24 h. Decreased testosterone and increased FSH and LH levels also occurred by 24 h suggesting direct damage to the testicular Leydig cells and loss of testosterone mediated negative feedback on gonadotropin release. Histological studies indicated that by day 6 significant damage occurred to the germ cells, with extensive exfoliation of spermatocytes and spermatids. This major mediator of critical illness may contribute to net body catabolism because of decreased endogenous androgen production. This adverse feature on reproductive function must also be considered when patients undergo cancer chemotherapy with this agent.

Preliminary evidence that taurolidine is anti-neoplastic as well as anti-endotoxin and anti-microbial

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Taurolidine is a chemical anti-endotoxin derived from taurine and formaldehyde. Following endotoxin challenge, taurolidine improves survival in animals by a direct action against either endotoxin or tumour necrosis factor (TNF). We addressed the ability of taurolidine to neutralize the effect of TNF *in vitro* in an ELISA MTT incorporation assay. Using the TNF sensitive fibrosarcoma 24T 2·5 we found that TNF-mediated cytotoxicity was not inhibited but was augmented by taurolidine.

Cell line tested	Concentration (μg/ml)	Inhibition of cellular metabolism (%)
24T 2·5	10	5·2
	25	43·6
	30	96·6
	$-+5\times10^4$U TNF	75·6
	$10+5\times10^4$U TNF	96·8

Taurolidine was then tested against multiple cell lines (two tumours, one normal) using a range of doses.

Cell line tested	Concentration (μg/ml)	Inhibition of cellular metabolism (%)
Foreskin		
Fibroblasts	20	31·7
LS174T (colon)	20	84·3
Jurkat (leukaemic)	20	84·6

Preferential activity against tumour lines was demonstrated at low doses with complete cellular inhibition of tumour, but not normal cells, occurring at doses >200 μg/ml. This preliminary data suggests that taurolidine may have anti-tumour activities independent of its immunomodulatory capability. The potential of this agent to neutralize tumour *in vivo* is now under investigation.

Influence of protein malnutrition on anti-tumour immune responses

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Tumours expressing tumour-associated antigens may elicit a host anti-tumour immune response. Such immunogenic tumours behave aggressively in protein-malnourished animals and we sought to determine possible underlying immunological mechanisms.

Six-week-old CFW mice ($n=200$) were fed a regular (24 per cent) or low (2·5 per cent) protein diet for 14 or 21 days. Cytotoxic T cells (CTL) were generated in 4d cultures of CFW (H-2k) and DBA/2 (H-2d) spleen cells; splenic natural killer (NK) cells were activated by Poly I C., and lymphokine-activated killer (LAK) cells were generated in interleukin-2 (IL-2; 200 U/ml x 3d)· cytotoxicity of these effector cells was measured against YAC-1 and P815 targets in 4 h chromium-release assays. Suppressor T cells (Ts) were measured by the ability of irradiated concanavalin A-activated T cells to inhibit a normal syngeneic concanavalin A proliferation resonse. Class II MHC expression, an index of antigen presenting cell (APC) capacity, was measured on peritoneal macrophages using indirect immunoflourescence and FACS analysis.

Protein (%)	Body wt (g)	CTL	NK	LAK	Ts	Class II MHC
24(14d)	28±1	85±2	26±5	47±8	54±10	15±2
2·5(14d)	22±1*	81±6	9±1*	48±12	50±5	7±2*
2·5(21d)	21±1*	80±5	15±2*	45±10	51±5	7±1*

CTL, NK and LAK expressed as percentage lysis at a 50.1 effector.target cell ratio; Ts expressed as percentage suppression; MHC expressed as percentage receptor expression. Results are given as mean±s.e.m. *$P<0·05$ versus 24% group, Student's *t* test

Protein malnutrition impaired class II MHC antigen expression and activated NK cell function. Impaired APC capacity may explain why immunogenic tumours behave aggressively in protein-malnourished animals. Importantly, this study also demonstrates for the first time that LAK cell generation for potential immunotherapy is not affected by acute protein malnutrition.

Osteomalacia: no association with prostate cancer

N.W. Clarke and N.J.R. George (introduced by D. Charlesworth), *Department of Urology, University Hospital of South Manchester, Manchester, UK*

Osteomalacia (abnormally thick seams of poorly mineralized osteoid in cancellous bone) has been implicated as a cause of bone pain in metastatic prostate cancer. This study examines the hypothesis by means of histomorphometric studies of skeletal tissue.

Seventy-three patients underwent transiliac trephine bone biopsy (66 after double labelling with tetracycline 250 mg qds for 3 days, repeated after 10 days). Bone cores (8 mm) were alcohol-fixed and sectioned undecalcified. Surface area, volume and thickness of unmineralized osteoid were measured by line intersect and point counting techniques using a Merz graticule. Mineralization rate was determined by measurement of distance between tetracycline-labelled calcification fronts.

Tumour free bone exhibited low values for osteoid surface (8·6±4·5, s.d., normal=18·3±2·5) and volume (1·2±0·92, normal=1·8±0·5) but standard seam thickness (0·13±0·8; normal=0·1±0·2). Mineralization rate was also depressed (0·45±0·16 miU/day, normal=0·7 miU/day.

Tumour infiltrated areas showed increased values for osteoid surface and volume (35·6±24·5 and 5·1±3·6) but normal thickness (0·15±0·9). Mineralization rate was grossly elevated where measurable (1·16±18 miU/day, $n=11$) and in the remainder very rapid mineralization produced diffuse tetracycline labelling of woven bone.

These observations confirm depressed osteoblast function in tumour-free bone and abnormally rapid mineralization within metastases. Neither finding is consistent with osteomalacia.

Massive lymph node metastases – a distinct sub-cell type of prostate cancer

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Prostatic cancer is known to express heterogeneous biological tumour behaviour. We observed that patients with widespread metastases in bone did not always, as might be expected, have metastases in lymph nodes, whilst other patients with massive node enlargement had no evidence of bone metastases. This pattern of tumour behaviour has been studied prospectively using computerized tomography (CT) in

127 patients with advanced prostate carcinoma: 60 (47 per cent, mean age 72 years) were positive. Of these 29 (48 per cent) had nodes 4 cm and 15 (25 per cent) had nodes 7 cm (maximum diameter 15 cm) Obstructive uropathy was observed due to nodes in 26 patients (43 per cent). Thirty eight (63 per cent) patients with lymph nodes also had bony metastases. There was a dramatic response to hormonal manipulation in patients with metastases in lymph nodes. Actuarial analysis showed 70 per cent survival at 2 years and 60 per cent at 5 years (cf patients with bone metastases only; 50 per cent and 13 per cent at 2 and 5 years respectively, $P<0\ 001$). Unexpectedly 6 of 38 patients with nodal and body metastases obtained a complete response.

The disparity in cellular behaviour and better prognosis in patients with metastases in nodes suggest that this is related either to a distinct cell type of prostate cancer or a favourable host response to the tumour

Cell saver in cancer surgery: removal of malignant cells from the red cell concentrate by filters

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The potential for the use of the cell saver in cancer surgery may be limited by its ability to retain malignant cells in the red cell concentrate (RCC)[1]. We have therefore investigated the use of two blood filters (Ultipor SQ40S 40μ blood filter and RC100 leucocyte removal filter (Pall Biomedical)) to determine whether tumour cells can be removed using these devices.

Units of banked blood were inoculated in duplicate with two tumour cell lines, colon cancer COLO 320 (25×10^6) and breast cancer SKBR3 (32×10^6). Blood was processed using the Cell Saver and then the RCC was subjected to no filtration, to filtration with SQ40S, or to filtration with RC100. After lymphoprep separation of the RCC, the layer where nucleated cells would be expected was examined for tumour cells and then cultered in appropriate media

Cell line	Cell count done	$10^{-6}\times$ Control (No /ml)	$10^{-6}\times$ SQ40S (No./ml)	RC100
COLO320	After lymphoprep	0 8	1 0	0
	After 7 days	5 0	4 2	0
SKBR3	After lymphoprep	0 7	0 2	0
	After 7 days	5 5	4 6	0

Thus cancer cells are effectively removed from the RCC by the RC100 but not by the SQ40S filter The cell saver in combination with RC100 filters may be valuable for use in cancer surgery even when the tumour is breached

1. Primrose JN, Ramsden C Is the use of the cell separator an alternative to blood transfusion with banked blood during cancer surgery? *Br J Surg* (in press)

Brain stem ischaemia induced by endothelin – a vasoconstrictor peptide

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Cerebral ischaemia and its sequelae remains a major clinical problem. Nevertheless the induction, in animal focal ischaemia models, of pathological flow levels remains problematic. We have previously shown endothelin, a 21 amino acid peptide, induces a significant reduction in cerebral vascular calibre for prolonged periods[1].

In this series we have examined the effects of injection of endothelin in adult male WKY rats into the cisterna magna. Under anaesthesia a stainless steel guide cannula was placed into the cisterna through which saline (2·5 μl) or endothelin (30 pmol in 2·5 μl saline) was injected one week later. [^{14}C]Iodoantipyrine autoradiography was used to measure regional cerebral blood flow (rCBF).

Endothelin induced a striking rise in MAP of 47·0±20 mmHg ($P<0\ 05$) and increased rCBF in rostral structures (*Table 1*). Despite this hypertensive response rCBF was markedly reduced to ischaemic levels in the brain stem (*Table 1*)

	rCBF (ml (100 g)$^{-1}$ min^{-1}	
	Control	Endothelin
Hypoglossal nucleus	115·2±3·0	29·4±12·2**
Rostral ventrolateral medulla	112 9±9·5	17·9±10·9**
Superior olivary nucleus	206 4±21·8	76·1±42·0*
Pons	108 3±4·5	61 7±24 0 n.s.
Ventral thalamus	190.7±11·6	252·0±28·9 n s.
Sensorimotor cortex	160·2±16·4	349·2±25 5**
Septal nucleus	130·6±18·7	190·1±10·6*

* $P<0{\cdot}05$, ** $P\ 0{\cdot}001$

This reduction in brain stem rCBF by endothelin is markedly greater than that seen with any previously studied endogenous agent

1 Robinson MJ and McCulloch J Contractile responses to endothelin in feline cortical vessels in situ. *J Cereb Blood Flow Metab* (in press).

Modification by mannitol of lower torso ischaemia induced lung injury by a non-osmotic mechanism

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Lower torso ischaemia leads to acute respiratory failure, thought to be dependent upon polymorphonuclear leucocytes (PMN), thromboxane (Tx), and oxygen free radicals. This study tests the ability of mannitol, a clinically available hydroxyl radical scavenger, to modify this lung injury. Anaesthetized rats ($n=48$) were randomized to receive intravenous saline ($n=12$), mannitol ($n=16$) or an equiosmolar solution of dextrose ($n=12$) during the 4 h of reperfusion following 4 h of bilateral hind limb tourniquet ischaemia. Five min after reperfusion, plasma (TxB_2) levels in the saline-treated group were 2372±788 pg/ml, relative to sham animals ($n=8$) values of 530±89 pg/ml ($P<0{\cdot}05$) After 4 h of reperfusion, plasma TxB_2 levels in the ischaemic saline-treated group were 3790±965 pg/ml, compared with 489±97 pg/ml in sham animal ($P<0\ 05$). Lung microscopy showed 108±15 PMN/20 high power fields (hpf), compared with 58±15 PMN/20 hpf in the sham group ($P<0\ 01$). At 4 h of reperfusion the wet to dry weight ratio of the lungs in saline-treated ischaemic controls was 5·0±0 1 compared with 4 0±0 1 in sham animals ($P<0{\cdot}01$). Mannitol treatment prior to tourniquet release gave the following reductions: Tx synthesis at 5 min and at 4 h of reperfusion (both $P<0\ 05$); leucosequestration ($P<0{\cdot}05$); and wet to dry weight ratio ($P<0\ 05$). Treatment with equiosmolar dextrose did not inhibit Tx synthesis, leucosequestration or lung oedema. The results indicate that mannitol reduces lower torso ischaemia induced lung injury by a non-osmotic mechanism, possibly related to its hydroxyl radical scavenging properties and/or inhibition of Tx synthesis.

Role of fine catheter peritoneal cytology and laparoscopy in the management of acute abdominal pain

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Both laparoscopy and fine catheter peritoneal cytology (FCPC) have been independently advocated as aids in the assessment of acute abdominal pain. Four hundred and eleven patients admitted to a district general hospital during a 10 month period, were managed using a standard protocol incorporating both these techniques.

After initial assessment by a surgical registrar, 151 patients were excluded from further progress through the protocol (<16 years old, definite diagnosis made or contra-indication to FCPC). The remaining 260 patients were placed in one of four management groups: (I) urgent operation (23 patients); (II) 'look and see' (40 patients), (III) 'wait and see' (46 patients); (IV) urgent operation not indicated (138 patients).

Eighty-eight of 99 patients (88 per cent) in groups II and III, where the need for operation was uncertain, underwent successful FCPC and 39 patients (39 per cent) underwent laparoscopy. In these patients the initial registrar management decision proved to be incorrect in 33 cases

(33 per cent) but, by following the protocol, the number of management errors actually made was reduced to 13 (13 per cent, $P<0\cdot001$). This would have been reduced to 8 per cent if the protocol had not been violated in five patients

This study demonstrates the effectiveness of a protocol using FCPC and laparoscopy to improve the management of patients with acute abdominal pain

Comparison of the effect of two different salvage systems on the 24 h survival of autotransfused red cells using a dual tracer technique

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Measurement of the survival of transfused red cells (RBCs) is vital to evaluate damage caused by cell salvage during intra-operative autotransfusion It is difficult to perform using a single isotope technique, as blood loss and fluid replacement dilute the isotope We have overcome this problem by the use of a dual tracer technique[1] and applied it to compare the survival of RBCs salvaged using two different auto-transfusion systems. Twelve patients undergoing elective aortic surgery had intraoperative autotransfusion, six with the Haemonetics cell saver and six with the Solcotrans device Preoperative RBCs were labelled with ^{111}I, salvaged RBCs taken from the reinfusion line were labelled with ^{51}Cr Both samples of labelled RBCs were returned to the patient immediately postoperatively Sequential blood samples were taken for isotope counting. The percentage survival of labelled RBCs was calculated at 1 and at 24 h for each isotope The isotope labelling technique was validated by measuring circulating red cell volume (RCV) and survival up to 24 h in four volunteers using separate aliquots of labelled RBCs. The difference in percentage survival of the two isotopes is outlined below The negative sign indicates elution of ^{111}I from the RBCs.

Group	1 h	24 h	RCV
Control	(−2 to 2)−0·5	(−10 to 1)−4·7	(0·8–1·2)0·73
Solcotrans	(−8 to 0)−1·8	(−12 to 0)−4·7	(0·0–0·6)0·32
Cell saver	(−2 to 8) 1·0	(−11 to −1)−6	(0·1–0·6)0·36

All differences between the groups were non-significant ($0\cdot5>P>0\cdot1$) using the Mann–Whitney *U* test Results given as mean with range in parentheses

These results suggest that the loss of autotransfused RBCs is small and that cell washing has no advantage with respect to the 24 h survival of RBCs

1. Holt JT, Spitalnik SL, McMican AE, Wilson G, Blumburg N A Technetium-99m red cell survival technique for *in vivo* compatibility testing *Transfusion* 1983, **20** 148–51.

Bile acid malabsorption in patients with postvagotomy diarrhoea: direct evidence following ^{75}SeHCAT scanning

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Hitherto, increased faecal bile acid secretion and symptomatic improvement following treatment with bile acid binding agents have provided indirect evidence of bile acid malabsorption in patients with postvagotomy diarrhoea The purpose of this study was to determine whether the ^{75}SeHCAT test could be used to detect bile acid malabsorption in patients with postvagotomy diarrhoea.

Seven-day ^{75}SeHCAT retention ratios were measured in five patients with unequivocal postvagotomy diarrhoea following truncal vagotomy and a drainage procedure The results were compared with an age-matched group of asymptomatic control patients ($n=4$) each of whom had previously undergone truncal vagotomy and drainage and a further group of normal volunteers ($n=6$)

The median ^{75}SeHCAT retention ratio in patients with postvagotomy diarrhoea was 2·0 per cent (range 0–9 per cent). In contrast, the median ^{75}SeHCAT retention ratio in asymptomatic controls was 29·0 per cent (range 26–61 per cent) and 38·0 per cent (range 19–70 per cent) in normal volunteers ($P>0\cdot05$, Wilcoxon, postvagotomy diarrhoea versus asymptomatic control and normal volunteers).

These results demonstrate, for the first time, that there is significant bile salt malabsorption in patients with postvagotomy diarrhoea and that ^{75}SeHCAT scanning is an effective screening test in these patients.

Intragastric and intraduodenal separation of ^{99m}Tc markers from fat in oral test meals

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Traditionally, ^{99m}Tc is used as a marker to measure transit and absorption of test meals. Separation of ^{99m}Tc from any component would make its use invalid We wished to assess whether ^{99m}Tc would separate from fat in an oral liquid test meal If separation occurred, could it be avoided by infusing the meal intraduodenally?

Nine normal volunteers swallowed a multilumen tube so that an infusion point was placed in the duodenum, and two aspiration points 40 cm apart in the upper jejunum. Each volunteer received two identical liquid meals labelled with ^{99m}Tc colloid, one swallowed, one infused intraduodenally (ID).

Jejunal aspirates revealed significant marker/fat separation in the oral meal, and this was greater than in the ID meal ($P<0\cdot05$, *F* test). ID meal fat/marker separation improved after 20 min, oral meal separation did not ($P<0\cdot001$, *F* test). In addition, ^{99m}Tc appeared to separate increasingly from fat during small bowel transit of the oral meal, but not the ID meal ($P<0\cdot05$, paired *t* test).

Fat content (g/100 g)	Meal	20–60 min collection	
		Prox. asp.	Dist asp
ID meal	4·31–5·88	2·37–5·84	0·66–4·41
Oral meal	4·05–4·85	0·88–15·17	0·36–25·05

Results are ranges of corrected fat concentrations for ^{99m}Tc dilution

^{99m}Tc cannot be used as a marker to measure transit and absorption of oral liquid meals, but can be used for intraduodenal meals

Correspondence

Peroperative observation of marginal artery bleeding; a predictor of anastomotic leakage

Sir

The paper by Novell and Lewis (*Br J Surg* 1990, 77 137–8) carries an important message, a message that is relevant to all colonic anastomoses whether they be hand-sewn or stapled. I was taught by the late Sir Hugh Lockhart-Mummery always to divide the marginal artery at the level of the proximal resection margin and observe the flow. I would suggest that anastomosis should not be performed unless there is pulsatile flow and that further resection of the proximal bowel is mandatory before any anastomosis is performed. I would further suggest that the authors' anastomotic leak rates when no flow was observed (100 per cent) and when there was no pulsatile flow (19 per cent) merely emphasizes the importance of flow, whatever the systemic factors The authors suggest however that although further resection may achieve a pulsatile flow this is not recommended if it results in an anastomosis under tension and that a proximal stoma may lessen the sequelae of subsequent anastomotic leakage I would suggest that no colorectal anastomosis will be under tension if the left colon is fully and properly mobilized and thereby a proximal stoma should not be required.

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Effects of somatostatin analogue SMS 201-995

Sir

Nott and colleagues (*Br J Surg* 1989; **76**: 1149–51) claim that somatostatin analogue SMS 201-995 given for 3 weeks will inhibit the growth of Walker carcinosarcoma cells implanted in the liver but not when implanted in the thigh They go on to claim that the effect seen on growth of these tumours in the liver must be indirectly mediated because they have shown a trophic response of these cells to SMS 201-995 treatment *in vitro*. Because they have been able to show alteration in hepatic reticuloendothelial function and portal venous flow they conclude that these findings probably explain the outcome of somatostatin treatment *in vivo*. This is simplistic and shows little grasp of tumour biology.

First, with regard to their *in vitro* study We are presented with the data of a single experiment in which a fixed number of Walker cells are exposed to a dose of somatostatin or saline and we are given the cell numbers at one time point (4 days) after the start of the study We are not told if the somatostatin was repeatedly administered to maintain a specific concentration throughout the experiment, since the concentration of active somatostatin analogue would rapidly change with hormone-receptor binding and turnover Similarly, we are given no information about relative cell numbers at any other time point which would suggest that they were fortuitous in their measurements at 4 days Such experiments only have any meaning when a full dose response curve has been established across both the physiological and pharmacological range of concentrations (femtomolar to micromolar concentrations) particularly as hormone dose response curves are often 'bell' shaped and addition of excess of hormone results in antagonism of responses seen at lower concentrations. Finally, simply to give us numbers of cells (without any data on the range of results) is inadequate· other means of objective measurement such as tritiated thymidine incorporation and the MTT assay are relatively straightforward and would give the reader more information on which to interpret the data.

Second, it is well established that somatostatin exerts its physiological effects on target organs both directly and indirectly through the inhibition of release of hormones that both stimulate and inhibit the target organ[1]. Differences in response between Walker tumour cells implanted in the liver and the thigh could well be explained by this mechanism since many peptide gut hormones (particularly the shorter chain molecules) are significantly metabolized on first pass through the liver, e.g. cholecystokinin[2] The relevance of this to the Walker tumour is unclear since nobody really knows what the origin of this cell line is, and so begs the question to the relevance of these experiments.

Third, the authors imply that their conclusions are supported by the negative finding of Savage *et al*[3] compared with a case report of vipoma regression in the liver following SMS 201-995 treatment. This completely ignores the rapidly increasing body of knowledge concerning the effects of somatostatin and its analogues on the growth of a large number of malignant tumours[4]

In conclusion the authors have made a number of interesting observations, some of which need to be interpreted with great care. It is a pity that these findings have been coupled with a poor discussion about the physiology of somatostatin which devalues their paper.

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1 Newman JB, Lluis F, Townsend CM jun. Somatostatin. In: *Gastrointestinal Endocrinology*, Thompson JC *et al.*, eds New York. McGraw-Hill Co , 1987· 286–99.
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3. Savage AP, Mathews JL, Adrian TE *et al.* Effect of a long acting analogue of somatostatin, SMS 201-995, on the development of intestinal tumours in azowymethane treated rats. *Carcinogenesis* 1987; **8**: 561–3.
4 Schally AV Oncological applications of somatostatin analogs *Cancer Res* 1988; **48**. 6977–85

Authors' reply

Sir

Thank you for the opportunity to reply to the letter by Mr Poston and Ms Gillespie criticizing our recent paper (*Br J Surg* 1989, **76**: 1149–51) in which we described the effects of SMS 201-995 on the growth and development of hepatic tumour derived by intraportal administration of Walker cells. We reported that suppression of the growth of hepatic tumour by SMS 201-995 was accompanied by a marked stimulation of hepatic reticuloendothelial system (RES) activity and alterations in liver blood flow. We concluded from these observations that alterations in hepatic RES activity and liver blood flow elicited by SMS 201-995, may at least in part, explain the suppression of hepatic tumour growth We are, however, careful to point out that other mechanisms could also be involved in the suppression of hepatic tumour growth by SMS 201-995, in particular inhibition of the release of hepatotrophic factors We also indicated that further studies are required, and indeed they are in progress to delineate more precisely the mechanism of action of SMS 201-995 in inhibiting the growth and development of hepatic tumour. It is clear from their letter that the correspondents have not understood, or even thoroughly read, our paper.

In recent years there have been numerous reports that peptide hormones stimulate the growth and development of a wide variety of tumorigenic cells both *in vitro* and *in vivo*. Furthermore, many tumour cells derived from both experimental and human neoplasms possess both low and high affinity somatostatin receptors, and in the majority of instances the hormone or its analogue SMS 201-995 inhibits the growth of such cells *in vitro* Thus somatostatin or SMS 201-995 may directly inhibit the growth of these tumour cells *in vivo* through an effect on the receptor, indirectly by inhibition of the release of the trophic hormone, or by a combination of these effects In order to establish whether Walker carcinosarcoma cells possessed somatostatin receptors which may have contributed to the suppression of their growth in the livers of rats treated with SMS 201-995, we incubated the cells with a range of concentrations of the analogue Lower concentrations of SMS 201-995 had no effect, but higher concentrations stimulated the growth of Walker cells *in vitro* We therefore included only one of the results instead of the full dose response curve in our paper, merely to illustrate that SMS 201-995 was not cytotoxic to the Walker cells. We concede that we should have included the standard deviation as well as the mean for both the control ($2{\cdot}80 \pm 1{\cdot}56 \times 10^5$ to $6{\cdot}32 \pm 1{\cdot}52 \times 10^5$) and SMS treated groups ($2{\cdot}66 \pm 1{\cdot}7 \times 10^5$ to $10{\cdot}06 \pm 1{\cdot}04 \times 10^7$).

The second point raised by Poston and Gillespie related to the studies in which the Walker cells were implanted into the thigh of the rats. They question the relevance of this part of the study since they argue that many of the hormones known to be trophic with respect to tumours are metabolized on first pass through the liver. However, the authors should be well aware that both somatostatin and SMS 201-995 act as 'endocrine poisons' almost completely inhibit the release of polypeptide hormones. Thus in animals treated with SMS 201-995, the portal blood would contain very little quantities of these gastrointestinal peptides and for this reason we could not eliminate inhibition of hepatotrophic hormone release as one of the possible mechanisms whereby the analogue inhibited the growth and development of liver tumour. Furthermore in rats with tumour implants in the thigh, hepatic function is preserved and the concentrations of these possible trophic hormones would be even lower in the peripheral blood than that in portal blood. In contrast, in control animals there would be no suppression of gastrointestinal hormone release and although many of the hormones are extracted on first pass through the liver, appreciable amounts can be detected in the peripheral circulation under certain physiological conditions, e.g., postprandially. Consequently, if any of these peptides are trophic to the growth of Walker cells *in vivo*, then one might expect enhanced growth of the tumorigenic cells implanted into the thigh. In fact this was not the case, and the weight of tumour in rats treated with SMS 201-995 was greater, but not significantly so, than those in the control animals.

Third, Poston and Gillespie claim that we have disregarded the growing body of knowledge concerning the effects of somatostatin analogues on the growth of a variety of neoplasms. We are in fact very well abreast with all this work, but apart from the one report on the possible regression of a metastatic vipoma[1], there have been no other investigations on the effects of such analogues on the growth and development of liver metastases.

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1 Kraezlin ME, Ch'ng JC, Ward SM, Carr DH, Bloom SR. Long term treatment of vipoma with somatostatin analogue resulting in remission of symptoms and possible shrinkage of metastases. *Gastroenterology* 1975, **88**: 185–7

Serum enzymes and other laboratory tests in acute pancreatitis

Sir

We heartily endorse the recommendations of Clavien *et al* in their scholarly and timely review (*Br J Surg* 1989, **76**. 1234–43) that computed tomography (CT) scanning is essential in the diagnosis of acute pancreatitis in patients with normal borderline enzyme elevations.

We question, however, whether the statement that an elevated total serum amylase has a 'sensitivity of approximately 80 per cent and a 70 per cent specificity' is generally applicable. Sensitivity and specificity are entirely dependent upon the diagnostic level at which the serum amylase is set. Thus, at 18 standard deviations above the mean of the normal range (1200 IU/l) in less than 2 per cent of all cases having a diagnostic measurement will this be misleading[1].

Frequently quoted by the authors is a recent study from Geneva[2] in which completely normal amylase was found in 19 per cent of 352 attacks of acute pancreatitis confirmed by CT. It is of some surprise that the diagnostic level of total serum amylase was taken as simply anything above the upper limit of normal (160 IU/l). We doubt if this is the general experience. In a series of 339 patients mostly included in recent studies[3–6], of whom 99 per cent were admitted within 24 h of an attack, we found the admission serum amylase (Phadebas method) to be elevated above the upper limit of normal (300 IU/l) in 99·1 per cent of cases and to have exceeded the diagnostic level (1000 IU/l) in 94·4 per cent. By 48 h after admission these figures were 72·3 per cent and 35·1 per cent respectively. The Geneva study reported also that 58 per cent of 132 alcoholic patients had a normal amylase. In our experience 98 per cent of 82 alcoholics had an elevated admission amylase but this was >1000 IU/l in only 84·1 per cent.

Clearly, where similar difficulties[1] are experienced by other units, we can see a major role for using serum lipase in conjunction with serum amylase. Otherwise we would suggest that lipase is used selectively rather than systematically as the authors suggest. We would, however, accept that both enzymes should be employed more widely in patients with suspected acute pancreatitis due to alcohol.

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2. Clavien PA, Robert J, Meyer P *et al*. Acute pancreatitis and normoamylasemia: not an uncommon combination. *Ann Surg* 1989, **210**. 614–20
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Authors' reply

Sir

We are grateful for the interest shown by Drs Neoptolemos and London in our review article[1]. They are particularly concerned about a recent prospective study from Geneva in which one of us was involved[2]. The purpose of that study was to define the incidence of normoamylasaemia on admission in patients with acute pancreatitis, by systematic use of contrast-enhanced CT scan, regardless of amylase values. It was found that 19 per cent of such patients were normoamylasaemic. Keeping the purpose of the study in mind it is not surprising that the amylase level of 160 IU/l was chosen since this is three standard deviations above the mean and therefore, by definition, includes 99 per cent of the values in a *normal* population. Are Neoptolemos and London suggesting that a higher level of amylase should have been taken as the cut-off in that study? If so the per cent of patients with 'normal' amylase would have been even greater and the resulting sensitivity worse.

They seem disturbed by the finding of the number of individuals with acute pancreatitis presenting with normoamylasaemia, and cite their own work[3,4] to suggest that the Geneva observations pertain only to the local circumstances in Geneva, Switzerland. However, in their work acute pancreatitis is defined in terms of an elevated serum amylase, i.e. 'serum amylase greater than 1000 U/l in the presence of a compatible clinical picture': their normal upper value was 300[3,4]. Of course almost 100 per cent of their patients will have a serum amylase greater than 300 U/l. In fact it is surprising that they all do not, given the definition of acute pancreatitis in their study. Therefore their comments about whether the results of the Geneva group reflect the 'general experience' are conjectural. We will only know about the pertinence and general applicability of the Geneva experience when other centres have examined normoamylasaemia in acute pancreatitis using the approach presented in the Geneva study. We also would like to point out that the statement by Neoptolemos and London that '58 per cent of alcoholic patients had a normal amylase' does not appear in the paper on normoamylasemia in pancreatitis[2], but rather it was stated that 'alcohol was incriminated in 58 per cent of normoamylasemic pancreatitis'.

The incidence of acute pancreatitis patients with normoamylasemia in the area of England studied by Neoptolemos and London may indeed be less than the 19 per cent in the Geneva study, but until they run the study, using a similar protocol, they cannot know the figure. We believe they might be surprised.

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1 Clavien P-A, Burgan S, Moossa AR Serum enzymes and other laboratory tests in acute pancreatitis *Br J Surg* 1989; **76**: 1234–43
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3 London NJM, Neoptolemos JP, Lavelle J, Bailey I, James D. Serial computed tomography scanning in acute pancreatitis: a prospective study. *Gut* 1989; **30**. 397–403
4 London NJM, Neoptolemos JP, Lavelle J, Bailey I, James D. Contrast-enhanced abdominal computed tomography scanning and prediction of severity of acute pancreatitis a prospective study. *Br J Surg* 1989; **76**. 268–72.

Endoluminal ultrasound for early detection of local recurrence of rectal cancer

Sir

The recent report by Mascagni *et al.* (*Br J Surg* 1989; **76**. 1176–80) demonstrated that endoluminal ultrasound can detect recurrence of rectal cancer in asymptomatic patients where other procedures such as digital examination, colonoscopy and computed tomography failed. Of the patients with local recurrence, only those detected by endoluminal ultrasound alone were suitable for further curative surgery Follow-up is as yet short but, even so, this may have important implications for follow-up of patients following excision of rectal tumours.

In general, the aims of out-patient follow-up are the detection of recurrent disease, the detection of metachronous disease, the collection of information for audit and for patient reassurance

Several studies have demonstrated that standard follow-up of colorectal cancer patients in the UK is ineffective in the detection of potentially curable recurrence. Cochrane *et al.*[1], in 1980, found that less than half of all recurrences were detected at a clinic visit in 180 patients despite a total of more than 2000 visits! An even lower figure of 25 per cent was reported by Hulton and Hargreaves[2]. Furthermore, merely increasing the frequency of routine follow-up appointments has not been shown to increase the rate of reoperation for cure[3].

Routine endoluminal and liver ultrasound techniques clearly require expertise and are more time-consuming and expensive than standard methods of follow-up, but increasingly might be expected to fulfil the first aim of follow-up, namely the detection of recurrence at a potentially curable stage Only those at high risk (i.e. Dukes' B and C) would need to be followed in this way and the majority of such recurrences would be detected within 2 years of primary operation.

The prevention of metachronous disease requires colonoscopy or contrast studies in the perioperative period and follow-up colonoscopy of those patients found to be polyp formers Again, this is expensive, time-consuming and requires experienced personnel

Clearly routine follow-up is an unreliable source of information for accurate audit as at most only 50 per cent of recurrences are detected at routine visits, presumably the remainder are referred back by their general practitioner. The reassurance gained by patients by visits to the clinic is only at the expense of anxiety in the period leading up to the visit.

The implication of this appears to be that routine follow-up, as it has been practised, is of little benefit to patients or their surgeons and that it could be replaced by more active programmes using ultrasound to detect potentially operable recurrence. To avoid excessive demands on radiology departments, surgeons should consider acquiring skills in ultrasonography.

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1 Cochrane JPS, Williams JT, Faber RG, Slack WW. Value of outpatient follow-up after curative surgery for carcinoma of the large bowel. *Br Med J* 1980; **280**: 593–5
2. Hulton NR, Hargreaves AW. Is long-term follow-up of all colorectal cancer necessary? *J R Coll Surg Edin* 1984; **34**: 21–4
3 Tornqvist A, Ekelund G, Leandoer L The value of intensive follow-up after curative resection for colorectal carcinoma *Br J Surg* 1982; **69**: 725–8

Self protection in surgery: the use of double gloves

Sir

In the paper about 'Self protection in surgery: the use of double gloves' (*Br J Surg* 1990; **77**: 219–20) it was mentioned that double gloving causes a decrease in sensitivity and dexterity and so increases the likelihood of injury. This can be overcome partially by wearing half size larger gloves on the inside rather than on the outside This not only stops the outer gloves slipping away and flapping around but also gives better tactile sensation. I have found this method of double gloving quite comfortable and have seldom felt that we were decreasing manual dexterity.

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Paget's disease

Sir

I was disappointed that your editorial process failed to correct an inadvertent error in the article by Dr Aktan and colleagues (*Br J Surg* 1990; **77**: 226–7).

Paget's disease of the breast and indeed Paget's disease of the bone (osteitis deformans) were described by Sir James Paget Bt. not as stated Sir William Paget Sir James Paget was one of the original 300 Fellows of the Royal College of Surgeons, and was Warden of the Medical College, and later Surgeon to St. Bartholomew's Hospital He was born, the eighth of 17 children, in 1814 and died in 1899 after a remarkable medical career. His early training as a naturalist and his great attention to detail contributed to his becoming perhaps the foremost surgeon of his generation.

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Book reviews

Atlas of Urologic Surgery

F. Hinman jun 310 × 240 mm. Pp 1057. Illustrated. 1989. London W B. Saunders £118 00

The accepted custom for most major surgical textbooks is that an editor commissions and coordinates the work of a number of colleagues. This *Atlas* represents one urologist's lifetime experience of open urological surgery Over many years Frank Hinman jun. made sketches of procedures that he had performed and which he had seen others perform With the help of one artist he has brought together a comprehensive account of all the non-endoscopic surgery that is performed in the field of paediatric and adult urology.

There are separate sections to cover the variety of operations which are available for the reconstruction, substitution or excision of different urological organs Each section is preceded by a brief account of indications and contra-indications, but no attempt is made to define the process of selection for any particular procedure. Complications and how to deal with them are also described.

Several features combine to make this an exceptional book One surgeon and one artist have created a uniformity of style which cannot be achieved in a multi-author test. As the author points out, to describe with pictures and text how to perform any operation is necessarily an impossible task; there is no substitute for watching, assisting or performing the procedure. Accepting this limitation, the talented duo have produced illustrations of the highest quality, which, together with the text, describe as comprehensively as possible how each procedure should be performed The author is courageous enough not only to describe his own techniques, even though the operation may have been described first by others, but he then invites commentaries from those urologists who are acknowledged international exponents of the particular operation. These commentaries are mostly constructive and informative, and create a lively forum for discussion. There is also a comprehensive list of references.

Frank Hinman jun believes that attention to detail is the foundation on which to base urological surgery. The same philosophy is transmitted to this masterly *Atlas* Although few trained urologists will come to perform regularly more than a small proportion of the procedures which are described, there will be few who could not benefit from studying the general principles and the detailed techniques which are included

This book, the distilled wisdom and experience of one urologist, provides a worthy successor to '*Principles and Practice of Urology*' which was written by Frank Hinman sen and will ensure that the name of Hinman continues to be respected by urologists throughout the world No urological library can afford to be without a copy and both those in training and those who are trained but are still wishing to learn should have a personal copy

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A Clinical and Pathological Atlas: The Records of a Surgeon in St. Vincent, The West Indies

A. Cecil Cyrus. 240 × 315 mm. Pp 260 Illustrated. 1989 York· A Cecil Cyrus £85 00 hardback Copies can be obtained from North Wolds Printers Ltd , Pocklington, York YO4 2QP, UK

This is a pictorial record of the many varied and interesting surgical cases that A Cecil Cyrus has seen and treated during the 27 years of his practice in the beautiful island of St. Vincent in the West Indies. This kind of surgery is disappearing in the UK and USA and we should be grateful to A Cecil Cyrus for recording these unusual pathological conditions. Surgeons of all kinds will find it fascinating looking at the pictures.

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Surgery of the Adrenal Glands

H William Scott jun 240 × 190 mm Pp 310. Illustrated 1989 Pennsylvania J B. Lippincott Co $59.50

Surgical texts may be likened to books on cookery or wine The larger text books attempt up to be comprehensive and can be likened to *Good Housekeeping* or *Mrs Beaton*. They tell us everything from how to choose a maid to how to prepare *agneu en croute*. The author or authors may be excused some detail and perhaps accuracy and we, the readers, are left to refine or experiment.

If we wish to specialize – let us say in southern cooking – we might turn to Mrs Dull[1] and read from her pages the personal touch of someone brought up in the Southern States with direct, hands on experience of all Southern States' food Should we expect her gumbo to be as well described and characterized as her mint julep? Should we allow her to obtain the services of others, for example, experienced in corn bread baking? Could all her writers be found in the Southern States or should we allow her to call upon an exile in Chicago who is *the* expert in the Carolinian methods of cooking okra?

Surgery of the Adrenal Glands is a specialized surgical text produced by writers from a single centre (by and large all are from Vanderbilt University). Does this result in 'a composite that concisely summarizes current knowledge of adrenal biology in health and disease with emphasis on the problems in clinical management that are the special concerns of the surgeon'? The clinical sciences of medicine and surgery at Vanderbilt allow this to be achieved since we can acknowledge the lifelong contributions to adrenal physiology by Dr Grant Liddle and adrenal surgery by Dr William Scott. The book is dedicated to Dr Grant Little who died last year

The surgery of the adrenal glands is very well covered (perhaps a little overdone!), with some duplication of text and figures (*Figures* 7 4 with 16.2; 7.5 with 16 6; 7.9 with 16 11 and 10 14 with 16 9)

The book provides the background to surgical disease (ingredients) with chapters on anatomy, physiology and biochemistry of the normal and diseased adrenals. It covers perioperative details (preparations) of imaging, preoperative blockade and anaesthetic considerations for each of the major tumour types The surgery, pathology and clinical results (the taste) are similarly described for each adrenal pathology (including congenital adrenal hyperplasia and non-functioning adrenal tumours)

Are there any shortfalls from not seeking the specialized exiles? These can only be minor and result in slight differences of emphasis (flavours). Examples might be. a fuller description of ^{131}I–MJBG imaging and its therapeutic possibilities, or greater mention of adrenal medullary disease in the multiple endocrine neoplasia type II syndrome and whether unilateral or bilateral adrenalectomy should be carried out.

There are over 170 illustrations many reproduced from earlier publications. One or two are spoiled by poor preparation, for example, scan dates and other unnecessary details on *Figure* 6.14, hand written markers on the 'busy' anatomy and embryology illustrations and the poor reproduction of *Figure* 2 2

For the adrenal gourmet, however, this book satisfies the appetite

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1. S R. Dull *Southern Cooking* New York Grosset and Dunlap, 1973

Notices and announcements

5–6 July 1990
Surgical Research Society Meeting
Southampton, UK
Information: Mr C D Johnson, University Surgical Unit, Centre Block 'F' Level, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK

9–20 July 1990
European Postgraduate Summer Course in Practical Nutritional Support of the Seriously Ill
Southampton, UK
Information Mr Brendan Moran, Department of General Surgery, Salisbury General Infirmary, Salisbury SP2 7SX, UK

12–14 July 1990
XVth International Update on Liver Disease
London, UK
Information. Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–15 July 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

15–21 July 1990
1990 Surgical Updating in Surgery and in Surgical and Oncological Disciplines
Milan, Italy
Information. Segreteria Organizzativa, MGR, Via Servio Tullio, 4-20123 Milano, Italy

22–27 July 1990
FASEB Summer Research Conference 'Physiology and Pathophysiology of the Sphlanchnic Circulation'
Colorado, USA
Information· Federation of American Societies for Experimental Biology, Splanchnic Circulation Conference, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

25–27 July 1990
British Association of Paediatric Surgeons XXXVII Annual International Congress
University of Strathclyde, Glasgow, UK
Information. Miss D. Grant, BAPS Administrative Secretary, Royal College of Surgeons, Nicolson Street, Edinburth EH8 9DW, UK

19–23 August 1990
Recent Advances in Oral Maxillofacial Surgery
Glasgow, UK
Information. Louise Deakin, Courses dept, The British Council, 65 Davies Street, London W1Y 2AA

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong
Information· The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

28 August–7 September 1990
Recent Advances in Respiratory Medicine
Edinburgh, UK
Information. Louise Deakin, Courses Dept, The British Council, 65 Davies Street, London W1Y 2AA, UK

1–6 September 1990
6th World Congress in Ultrasound
Copenhagen, Denmark
Information Torben Larsen, Dept of Gynecology, Herlev Hospital, DK-2730 Herlev, Denmark

6–8 September 1990
2nd Congress of the European Association of Video-Surgery
Turin, Italy
Information. Professor A. Gaetini, Torino Esposizioni Corso Massimo D'Azeglio 15-10126 Torino, Italy

14–17 September 1990
Annual Meeting of RCPSC
Toronto, Canada
Information Anna Lee Chabot, Head – Meetings and Assemblies Section, Office of Fellowship Affairs, The Royal College of Physicians and Surgeons of Canada, Toronto, Canada

20–21 September 1990
IV Annual Meeting of the European Society for Vascular Surgery
Rome, Italy
Information: Paolo Fiorani, Department of Vascular Surgery, University of Rome, School of Medicine, Policlinico Umberto 1, 00161 Rome, Italy

23–28 September 1990
Comprehensive Review and Update of What's New In Vascular Surgery
Santa Monica, California, USA
Information: Dr W. S. Moore, Professor of Surgery, Section of Vascular Surgery, UCLA School of Medicine, PO Box 24901, Los Angeles, California 90024-0901, USA

25–28 September 1990
1st International Conference on Ultrasound Angiography
London, UK
Information· Mr K N Humphries, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

26–28 September 1990
Annual Scientific Meeting
University of Manchester
Information: Ann Muir, Association of Anaesthetists, 9 Bedford Square, London WC1B 3RA, UK

1–4 October 1990
Eurochirurgie: 92e Congres Francais de Chirurgie
Paris, France
Information: Secretariat Administratif, CONVERGENCES-AFC 90, 120 avenue Gambetta, 75020 Paris, France

3–6 October 1990
Principles of Colon and Rectal Surgery
Minneapolis, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455, USA

7–12 October 1990
Future Conventions of the American College of Surgeons
San Francisco, USA
Information· Fred C Spillman, Convention Manager, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

17 October 1990
Recent Developments in Intraoperative and Endoluminal Ultrasound
Oxford, UK
Information: Mr Mortensen, Consultant Surgeon, John Radcliffe Hospital, Oxford OX3 9DU, UK

23–31 October 1990
Clinical Anaesthesia in the 1990s
Bristol, UK
Information· Louise Deakin, Courses Dept, The British Council, 65 Davies Street, London W1Y 2AA, UK

2 November 1990
Management of Complications Following Vascular Surgery
Newcastle-upon-Tyne, UK
Information Mr J Chamberlain, Ward 7 Office, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK

3–7 November 1990
State of the Art in Digestive Surgery
Delhi, India
Information· Convention Centre, Hotel Taj Palace Intercontinental, Sardar Patel Marj, New Delhi 110021, India

13–16 November 1990
2nd International Interdisciplinary Symposium
Vienna, Austria
Information· Peritoneum and Peritoneal Access (PAX), F Schulz, c/o Vienna Academy of Postgraduate Medical Education and Research, Alser Strasse 4, A-1090 Vienna, Austria

6–8 December 1990
1st International Symposium on Benign Breast Disease and Chemoprevention of Breast Cancer
Genoa, Italy
Information· Oncologia Clinica, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10, 16132 Genova, Italy

11–13 December 1990
5th International Workshop on Therapeutic Endoscopy
Hong Kong
Information. Joseph W C Leung, Senior Lecturer in Medicine, Prince of Wales Hospital, Shatin, Hong Kong

19–20 January 1991
Hong Kong Surgical Forum
Hong Kong
Information· Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

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